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This manuscript is written as part of the Symposium titled, "Exertional Heatstroke: An International Perspective," presented at the annual meeting of the American College of Sports Medicine. The purposes of this manuscript are to review the scientific literature and describe original results, in an attempt to summarize our knowledge of the time course and extent of recovery from heatstroke, the heat acclimation ability of prior heatstroke patients, and the factors which may have predisposed these patients to heatstroke. One out of 10 prior heatstroke patients (PH) was heat intolerant, upon initial testing; upon later testing, this subject showed normal heat tolerance (at 11.5 months post-heatstroke). Nine out of 10 PH were normal, in virtually all measurements. The importance of situational factors is highlighted by the fact that none of the 10 PH in this investigation were hereditarily heat intolerant.

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Time course of recovery and heat acclimation ability of prior heatstroke patients

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Running Head: Heatstroke Patient Recovery and Heat Acclimation

[7 tables, 8 figures]

Abstract

Our understanding of the time course of recovery from exertional heatstroke (EH) and the heat acclimation ability of prior EH patients (P) is limited. This manuscript reviews previous findings regarding recovery from EH, and presents original research involving the heat acclimation ability of 10 prior EH patients (PH) and five control subjects. Heat acclimation, by definition, distinguishes heat intolerant P from heat tolerant P. Nine PH exhibited normal heat acclimation adaptations ($40.1^{o}C$, 7 d, 90 $min \cdot d^{-1}$), thermoregulation, sweat gland function, whole-body sodium and potassium balance, and blood values at 61 $\pm$ 7 d after EH; one PH (subject A) did not adapt to exercise in the heat, was defined heat intolerant, but subsequently was declared heat tolerant (11.5 months post-EH). Three PH exhibited large, unexpected increases in serum CPK levels, which resolved upon subsequent testing, and were probably related to their detrained state and the exercise which they performed. It was concluded that: (1) sleep loss and generalized fatigue were the most common predisposing factors for PH; (2) recovery from EH was idiosyncratic and may require up to one year, in severe cases; (3) PH were not hereditarily heat intolerant, prior to EH; (4) no measured variable predicted recovery from EH, or heat acclimation responses; (5) heat intolerance occurs in a small percentage of P, and may be temporary or permanent.

KEY WORDS: exertional heatstroke, heat acclimation, hyperthermia, creatinine phosphokinase, lactic dehydrogenase, aspartate aminotransferase, alanine transferase

Introduction

The extent of the multi-system tissue injury of heatstroke is highly individualized and the rate of recovery from heatstroke is unique to each individual. Keren et al. (29), for example, observed that the heat intolerance of one male, who experienced heatstroke twice, was temporary and was resolved five months after the second heatstroke episode. Similarly, Bianchi et al. (11) found a variety of histological abnormalities in the liver tissue of two distance runners, which were resolved 11-12 months after heatstroke occurred. Other laboratory trials (20,48) however, demonstrated that some prior heatstroke patients (P) were heat intolerant 2 - 5 years after they experienced heatstroke. This presents a difficult task to physicians, as they attempt to evaluate the ability of recovering P to return to exercise in hot environments. Clearly, when P are declared "clinically normal", they still may be heat intolerant. Heat intolerance has been defined as an inability to adapt to exercise in a hot environment (20,43,50), suggesting that classical heat acclimation adaptations do not occur in heat intolerant P. Nearly complete heat acclimation adaptations, to a given level of exercise-heat stress, are acquired by healthy humans in seven to 10 days and result in improved ability to exercise and live in the heat (51). However, the exact differences among the heat acclimation adaptations of heat intolerant P, heat tolerant P, and normal humans have not been clearly described.

Although many case reports exist (8,10,29,41,49,55), only three previous controlled laboratory investigations (20,45,48) have involved P. None of these reported comparisons of fluid-electrolyte and cardiovascular data, or thermoregulatory responses of P versus control subjects, during heat acclimation trials. The current manuscript reviews the findings of these investigations and case reports involving P, but primarily focuses on the evaluation of 10 prior

exertional heatstroke patients (PH) in our laboratory. The purpose of this original research was to describe the recovery from exertional heatstroke and the heat acclimation ability of PH, during repeated days of exercise-heat stress. The factors which may have predisposed PH to heatstroke also were examined, because it was not known whether PH were hereditarily heat intolerant at the time of heatstroke, or whether their heatstroke resulted from situational or host factors (e.g. pyrexial illness, inadequate heat acclimatization, sleep loss). The time elapsed between the exertional heatstroke episode and laboratory testing (mean $\pm$ SE: 61 $\pm$ 7 days) was a unique feature of this investigation considering the fact that other laboratory studies (20,45,48) evaluated P 2 - 5 years after they had experienced heatstroke.

Methods

Ten male PH participated in this investigation, which was approved by the local institutional review board, after giving their informed, written consent. PH were declared clinically normal (e.g. absence of symptoms, no abnormal laboratory values) by their attending physicians, completed a treadmill exercise stress test with no electrocardiographic abnormalities, and arrived at this laboratory 61 $\pm$ 7 days after exertional heatstroke; all PH were military personnel (4 officers, 6 enlisted). Medical records were obtained from the attending physicians. The criteria used to verify exertional heatstroke were similar to those which the authors published earlier (25): rectal temperature $\geq$ 40° C, altered mental status, and elevated creatinine phosphokinase (CPK), lactic dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine transferase (ALT). PH completed a Predisposing Factors Questionnaire prior to testing, to identify factors which may have influenced their health and performance during the five days prior to heatstroke.

In this manuscript, heat acclimatization occurs in natural environments, whereas heat acclimation occurs in artificially controlled environments. Prior exertional heatstroke patients, in general, are denoted by the abbreviation P, while the 10 prior exertional heatstroke patients who participated in this investigation were identified as PH. The data of subject A were eliminated from PH, in some statistical analyses (see results below). PH were subdivided into groups P1 and P2, for the sole purpose of enzyme data analysis (see results below).

The physical characteristics of PH are presented in Table 1. Two PH (subjects A and G) had previously experienced heat exhaustion, but none had a history of heatstroke, childhood febrile seizures, or malignant hyperthermia. A group of five healthy males (Control) undertook the same protocol that PH did (Fig. 1). The mean ($\pm$ SE) characteristics of Control were as follows: age - 25 $\pm$ 4 yr (range: 18 - 42 yr), height - 177 $\pm$ 4 cm, body mass - 78.250 $\pm$ 7.800 kg, surface area - 2.00 $\pm$ 0.09 m^2, mass-to-surface area ratio (M/SA) - 39.7 $\pm$ 1.8 $kg \cdot m^{-2}$, body fat % - 14.7 $\pm$ 1.9 %, maximal aerobic power ($\dot{V}O_2max$) - 52.11 $\pm$ 2.37 $ml \cdot kg^{-1} \cdot min^{-1}$. None of these characteristics were statistically different from those of PH (Table 1). All subjects were unacclimatized at the onset of laboratory testing; at the time of heatstroke, five PH were judged to be heat acclimatized, based on subject descriptions of activity and heat exposure. Subject A repeated this protocol (Fig. 1) three times, to observe improvements in his ability to acclimate to heat; subject F performed three iterations of this protocol, and subjects E and G performed two iterations, in an attempt to monitor progressive reductions in serum CPK values.

TABLE 1

FIGURE 1

All heat acclimation measurements were conducted in an environmental chamber maintained at 40.1 $\pm$ 2.3°C db, 23.8 $\pm$ 1.4°C wb (Fig. 1). Heat acclimation trials consisted of 90 minutes of treadmill walking (5.6 $km \cdot h^{-1}$, 5 % grade, 45 $\pm$ 2 % of $\dot{V}O_2max$) for seven consecutive days. Subjects were

instructed to drink large quantities of water before, during, and after each trial to insure adequate hydration, and were requested to produce a minimum daily urine volume of 2 l. A trial was terminated if heart rate (HR) exceeded 180 beats·min^{-1}, if rectal temperature (T_{re}) exceeded 39.0°C, or if T_{re} increased $\geq$ 0.6°C during any five minute period. T_{re} was measured via rectal probe inserted 8 cm beyond the anal sphincter, and mean weighted skin temperature (T_{sk}) was calculated by using a three site derivation. The rate of body heat storage was calculated using the following formula:

$$\text{Heat Storage } (\text{Cal}\cdot\text{m}^{-2}\cdot\text{h}^{-1}) = M\cdot S\cdot\Delta MBT\cdot SA^{-1} \qquad \text{(Eq. 1)}$$

where M is body mass (kg), S is the specific heat constant (0.83 $W\cdot h^{-1}\cdot kg^{-1}\cdot{}^{o}C^{-1}$), ΔMBT is the change in mean body temperature ($0.8\cdot T_{re} + 0.2\cdot T_{sk}$), and SA is surface area (m^2) (14). The number of heat activated sweat glands (HASG) was determined at the end of exercise, by covering an area of skin over the scapula with a layer of vaseline petroleum jelly. Microphotography (35mm) was used to provide a permanent record of the number of active sweat glands (appearing as a bead of sweat) per cm^2. In addition to the collection of thermoregulatory and cardiovascular data, several blood factors were measured, including clinically relevant enzymes (CPK, LDH, AST, ALT) and percentage plasma volume change (ΔPV%) from B to day 7 (16). The physiological data described in Figure 1, including sweat electrolyte collections via whole-body washdown, were obtained using standard laboratory procedures described by the authors previously (3,4).

Two-way ANOVA with Newman-Keuls post hoc comparisons were used to identify significant differences between PH and Control, and between heat acclimation days. Statistical correlation coefficients were calculated via multiple linear regression analysis. Although day 7 was the end point of heat acclimation, the data for day 6 are reported in Figures 2 and 3, and Table 5 because of

circumstances beyond the investigators' control on day 7 (i.e. equipment malfunction, subject illness). It should be noted that all subjects underwent a 15 min step test (48) in a temperate environment (25.8°C) two days prior to the start of the heat acclimation; also a six hour trial was performed (results not shown) in the heat (3 h walking, 3 h rest) by all subjects on the day prior to the initial 90 min heat acclimation trial (day 1 in Fig. 1). The methods of this step test (4) and six hour trial (6) are published elsewhere, and the results are currently in preparation.

Results

Situational factors present at the time of heatstroke are summarized in Table 2. Although dry bulb temperatures were moderate, relative humidity was high in every reported case. Only 2 PH (subjects C and J) were involved in a competitive event; all others were participating in routine group physical training. Subjects G and H experienced heatstroke during the same training run. Six PH (subjects E through J) were involved in specialized military training, which required an abrupt change in lifestyle (e.g. intense physical activity, altered sleep pattern, frequent psychological stress). TABLE 2

Table 3 lists selected characteristics of PH during each heatstroke episode and subsequent hospitalization. Coma or disorientation was present in all PH, although the duration varied widely. Peak levels of CPK, LDH, AST, and ALT were all above the normal range. The duration of altered mental status was not significantly correlated ($p > .05$) with either the peak serum enzyme levels during hospitalization (Table 3) or the peak serum enzyme levels observed during heat acclimation trials. Sleep loss, generalized fatigue, a long exercise bout (or frequent exercise sessions each day), and a long heat exposure were the most prevalent predisposing factors acknowledged by PH (Table 4). TABLE 3 TABLE 4

Exertional heatstroke may be the most serious threat to life during vigorous exercise (55), and awareness of the signs and symptoms of heat illness is essential for anyone who trains (subjects E through J, Table 2) or competes (subjects C and J, Table 2) in a hot environment. Six out of 10 PH, for example, recognized prodromal signs of impending illness (Table 4), but only three of these men (subjects B, G and I) recalled such signs prior to the day of heatstroke. Headache, dizziness, lack of coordination and disorientation were frequent complaints. These agree well with the prodromal signs described in the American College of Sports Medicine Position Stand titled, "The Prevention of Thermal Injuries During Distance Running" (2), and with the reports of other investigators (18,44). As noted previously (5), complaints of hyperthermia were conspicuously absent.

The HR and T_{re} responses of PH and Control on day 1 and day 6 of heat acclimation are illustrated in Fig. 2 and Fig. 3, respectively. Both PH and Control showed significant decreases in HR ($p < .05$) and T_{re} ($p < .025$) by day 6; this indicated that nine PH acclimated normally, and were defined as heat tolerant. Subject A was defined as heat intolerant, because he was unable to complete the full 90 min trial on days 1 - 7, due to T_{re} of 39.0°C, using the definition of Strydom (50) and others (20,43). Data for Subject A were deleted from the PH group and the statistical analyses of heat acclimation trials (Tables 5 - 7, Fig. 2 and 3) were performed using $n = 9$ for PH. Subject A was scheduled for a second and third iteration of this protocol, at seven and 11.5 months following heatstroke, due to his inability to acclimate. He was heat intolerant during the second iteration, but exhibited improved HR and T_{re} adaptations during the third iteration, and was defined heat tolerant at that time. The change in final HR and final T_{re} (day 1 versus day 6) for PH during heat acclimation (Fig. 2, 3) were not significantly correlated ($p > .05$) with either the

FIG. 2
FIG. 3

TABLE 5, 6, 7

peak serum enzyme levels during hospitalization (Table 3) or the peak serum enzyme levels observed during heat acclimation trials (Fig. 4 - 7). FIG. 4, 5, 6, 7

Table 5 summarizes selected thermoregulatory measurements made during 90 min heat acclimation trials, for the nine heat tolerant PH and Control. No significant between-day differences were observed because subjects were acclimated for 7 days only. Had PH and Control been exposed to heat for a longer period (i.e 14 days), significant between-day differences (e.g. sweat rate, sweat sensitivity, T_{sk}) would probably have been observed (56). Mean submaximal oxygen uptake ($\dot{V}O_2$submax) on day 1 was lower ($p < .025$) in PH (22.48 ± 0.87 $ml \cdot kg^{-1} \cdot min^{-1}$) than in Control ($26.11 \pm 0.93$ $ml \cdot kg^{-1} \cdot min^{-1}$); the corresponding mean respiratory exchange ratios were higher ($p < .025$) in PH (0.92 ± 0.02) than in Control (0.84 ± 0.03). Mean final rating of perceived exertion (RPE) was not significantly different, between groups or between days (range: 10 - 11).

Table 6 describes whole body sodium and potassium balance during heat acclimation. It was concluded that no substantial sodium or potassium deficit occurred in either PH or Control, as a result of daily 90 min trials. There were no between-day or between-group differences in mean pre-exercise body weight, 24-hour caloric intake, 24-hour urine volume, or urine specific gravity. All mean urine specific gravity values were ≤ 1.020 on all days, for PH and Control.

Pre-exercise blood values, including mean corpuscular hemoglobin concentration (MCHC) ($g \cdot dl\ rbc^{-1}$), are presented in Table 7. ANOVA indicated that there were no significant differences between PH and Control in any of these blood measurements. Other analyses (not shown) indicated that calcium, blood urea nitrogen, uric acid, and total bilirubin were found to be within normal ranges on all days, for PH and Control. The $\Delta PV\%$ were positive and large in both groups, by day 4 of heat acclimation.

The analysis of clinically relevant enzyme data (CPK, LDH, AST, ALT) indicated that two distinct PH groups existed. Three PH (subjects E, F, G) exhibited unexpected, large CPK elevations, and were evaluated as a group (P2) separate from the other seven PH (P1), who exhibited normal serum enzyme values throughout iteration 1 of the heat acclimation process (Fig. 4 - 7). CPK was used to identify group P2 because it is an indicator of muscle injury (38) and malignant hyperthermia (28). Although Subject A was defined as heat intolerant during heat acclimation trials, he exhibited normal CPK, LDH, AST, and ALT values throughout the investigation, and was included with group P1 for enzyme data analysis. Subjects E, F and G all returned to repeat this protocol a second time (iteration 2), approximately three months after their first testing (iteration 1); subject F returned for a third series of testing (iteration 3) because his CPK, LDH and AST levels were elevated during iteration 2. Most statistical differences between P2 and P1 (or Control) occurred on day 1 of heat acclimation, during iteration 1 of this protocol (Fig. 4 - 7). These rises in serum CPK, LDH, AST and ALT probably resulted from the trials conducted prior to day 1 of heat acclimation (see methods).

Figure 8 presents the serum CPK, LDH, AST, and ALT levels for one member of P2 (Subject F), during iterations 1, 2, and 3 of the protocol. Subject F performed iterations 1, 2, and 3 at 40 d, four months, and eight months after heatstroke. Although CPK, LDH, AST and ALT were elevated during the first and second iteration, they were within the normal range during the entire third iteration. This trend toward normal serum enzyme levels also was observed for subjects E and G.

FIG. 8

Discussion

The scientific and clinical literature identify four general categories of individuals which experience heatstroke: non-exercising, older patients with underlying systemic illness (e.g. cardiovascular disease) in hot environments (31); religious pilgrims (1,32) who undertake mild exercise (i.e. walking) in hot environments for many hours on consecutive days; non-acclimatized, moderately fit individuals exercising in warm, humid ($\geq$ 70 % rh) environments (8,29,49); and highly trained, motivated individuals exercising at high intensities in the heat (10,44,55). The first group experiences classical heatstroke (31), and the latter three groups experience exertional heatstroke; the PH in the current investigation (Table 1) represent the latter two groups. It is interesting to note that the incidence of signs and symptoms, and elevations of serum enzyme levels, are subtly different in these four groups, depending on the involvement of exercise, dehydration, and the duration of hyperthermia (1,22,25,29,47). Shibolet (47) recognized this fact in 1976, when he described 20 "light" and 16 "severe" cases of exertional heatstroke. In the light heatstroke cases, coma was less prolonged, and hyperthermia fell rapidly within an hour; biochemical evidence of multiple system involvement was still distinct, however. Severe heatstroke cases, in contrast, were often moribund on admission and died early of central nervous system damage, before the multiple system disruption became evident (47). The primary difference between light and severe heatstroke may be the length of time between collapse and the initiation of cooling therapy (8,13,22), recognizing that some cooling techniqus may cool the body faster (12,44).

THE TIME COURSE OF RECOVERY

The comparison of the heat acclimation data of PH and Control (Fig. 2, 3 and Tables 5, 6, 7) demonstrated that nine PH were physiologically normal. In these nine PH, the designation of "clinically normal" was equivalent to "heat tolerant", at 61 $\pm$ 7 d after exertional heatstroke (range: 25 - 99 d, see Table 1).

This was not true for subject A, who was unable to complete 90 min trials on all days, due to a final T_{re} in excess of 39.0°C, in a manner similar to the heat intolerant P described by Shapiro (45) and Shvartz (48), in spite of normal sodium and potassium balance (Table 6), and blood values. Recognizing that heat intolerance may be temporary (29), subject A repeated this protocol five months after his initial evaluation; again, he showed no final HR and final T_{re} reductions during seven days of heat acclimation. This led to a third iteration of the protocol, during which his final HR and final T_{re} values decreased during heat acclimation, as expected. The recovery from exertional heatstroke-induced hepatic injury in two distance runners was reported by Bianchi et al. (11) in 1972. Liver biopsies were taken at five time points, ranging from nine days to 11 - 12 months after heatstroke. Complete histological and biochemical recovery was not observed until the final observations were made, nearly one year after heatstroke. Although this lengthy recovery time agrees well with the recovery of heat acclimation ability in subject A (at 11.5 months post-heatstroke), this does not indicate that he had severe liver damage. In fact, the serum biochemical markers which correlate well with the severity of liver injury (i.e. LDH, AST, ALT) (30), were elevated in subject A during hospitalization, but were below the mean for PH (Table 3), and were within the normal range during iterations 1, 2 and 3 of this protocol. The following two factors reportedly indicate an unfavorable prognosis, following exertional heatstroke: duration of coma for longer than 2 h, and elevation of AST over 1000 $U \cdot l^{-1}$ during the initial 24 h (47). However, neither of these factors served to distinguish subject A from the other PH, during iteration 1 of this protocol. In fact, the serum enzyme values of subject A were normal during heat acclimation.

SERUM ENZYME ELEVATIONS

Serum CPK levels indicated that three PH (subjects E, F, G) had unexpectedly high CPK values (838, 5625, 958 $U \cdot l^{-1}$, respectively; normal range: 33 - 213 $U \cdot l^{-1}$), were asked to return for future testing, and were treated separately (as group P2) from the other seven PH (group P1) during enzyme data analysis (Fig. 4 - 7). Isoenzyme assays indicated that the CPK in the serum of group P2 originated in muscle tissue (> 98 % m-m band), in all cases. These CPK elevations during exercise-heat tolerance may be explained in three ways. First, CPK elevations may have been related to malignant hyperthermia, a hereditary condition which shares many symptoms with heatstroke, including elevated serum CPK. Malignant hyperthermia has been proposed as a factor which predisposes certain individuals to heatstroke (28,31,47). The fact that CPK levels returned to the normal range in group P2 (iteration 2 or 3), and were normal in group P1, essentially discounts this explanation. Only subject E was tested for malignant hyperthermia (muscle biopsy) between iteration 1 and 2, and the results were negative. Second, elevated CPK levels may have been a sequela of heatstroke, in the form of increased membrane permeability and muscle damage (24,25,27); this explanation suggests an increased risk of experiencing a second heatstroke. Third, elevated CPK levels may have resulted from inactivity and detraining in P2, because of restrictions on physical training and heat exposure following heatstroke (see the description of subject E below). Although the second hypothesis cannot be ruled-out, the third hypothesis is supported by the following evidence. (1) The serum CPK levels of one Control subject (42 yr old) were elevated during heat acclimation and peaked at 659 $U \cdot l^{-1}$ on day 4. This resulted in the day 4 elevation of mean CPK level shown in Figure 4 and indicated exercise involvement. (2) A 15 min step test (results not shown) in a temperate environment (25.8^{o}C) was performed by PH two days prior to the start of heat acclimation (see methods). A similar step test (38) resulted in

unexpected, large serum CPK elevations (i.e. 3,500 - 10,000 $U \cdot l^{-1}$), four to five days after it was performed. They were explained by the fact that bench-stepping differs from most exercise tests, in that it involves eccentric contractions in which the active muscle is lengthened. (3) The changes in CPK, LDH, AST and ALT values during heat acclimation (Fig. 4 - 7) did not follow the course of serum enzyme changes typically seen after heatstroke (Table 3), which is characterized by a rapid rise of CPK relative to the delayed rise and fall of LDH and the transaminases. Wyndham et al. (57) came to this same conclusion, after measuring serum enzymes in unacclimatized and acclimatized males, who performed 4 h of exercise under severe heat stress.

Only one research team reported the serum enzymes of P following exertional heatstroke (10), but their data indicated little about the time course of recovery. Figure 8 depicts the serum enzyme levels of subject F and illustrates the trend which was noted in all members of group P2. This trend involved reductions of CPK, LDH, AST and ALT, from iteration 1 to iteration 2 or 3. This trend hypothetically may be explained by the restoration of normal membrane/organ function, increased physical training after each successive iteration, or combinations of these factors.

HEAT ACCLIMATION, HEAT INTOLERANCE

Information regarding the heat acclimation ability of P is deficient. The enlightening case reports of Sohar et al. (49), Wyndham (55), and Assia et al. (8), as well as the clinical findings of Costrini et al. (13) did not examine heat intolerance subsequent to heatstroke, in any way. Robinson and colleagues (41) were the first to report physiological responses of P, when they exposed two males to treadmill exercise, at 5 months and 8 months after heatstroke. Although partial heat acclimation data were presented, no conclusions regarding the heat acclimation ability of P could be made. The case report of Keren et al.

(29) described a 19-year old farmer who experienced exertional heatstroke twice within 17 days. He performed a heat tolerance test (40W, 40°C, 3 h), one month and five months subsequent to his second heatstroke. The ability of this young man to acclimate to heat was not evaluated. In terms of controlled laboratory studies which contained adequate sample sizes, only three previous publications have reported the physiological responses of P. Shvartz et al. (48) observed four heat intolerant P during 15 min (23°C db, 16°C wb) and 60 - 100 min (39.3°C db, 30.3°C wb) of bench stepping exercise. Shapiro et al. (45) reported the heart rate, rectal temperature and sweat rate of nine P, during 3 hours of bench stepping exercise at 40W, in ambient conditions of 40°C db and 23°C db. Utilizing a similar protocol, Epstein and colleagues (20) focused on heart rate and rectal temperature responses of four heat intolerant P and five heat tolerant P, during a 3-hour trial. These three studies did not report comparisons of the fluid-electrolyte, cardiovascular, or thermoregulatory responses of P versus control subjects, during daily heat acclimation trials.

The authors believe that longitudinal observations are essential in describing the heat tolerance of P, for two reasons. First, the phrase "heat intolerance" has been used in a wide variety of contexts (7). In this manuscript, heat intolerance is defined as the inability to adapt to exercise in a hot environment (20,43,50). A longitudinal research design is superior in studies involving P, because P typically have heat exposure and physical training restrictions imposed upon them by their physicians; these restrictions result in detraining and degrade performance during an exercise-oriented heat stress test. Second, the performance of P on a single heat tolerance test can be altered within days by physical training, heat acclimation, and a variety of mutable host or situational factors (7,51).

Using these concepts, Senay and Kok (43) described the detection of heat intolerant miners, by measuring their ability to acclimate to repeated days of

exercise in hot, humid environments. Wyndham (54) and Strydom (50) reported that two to five per cent of these recruits were innately heat intolerant. In the current investigation, it was not known whether PH were members of this heat intolerant group, at the time of their heatstroke, or whether situational/host factors predisposed them to heatstroke. Nearly complete heat acclimation to a given level of exercise-heat stress classically has been associated with reduced heart rate and core body temperature (21,51). Figures 2 and 3 illustrate the HR and T_{re} of PH and Control, at the end of 90 min trials on days 1 and 6. Because nine PH exhibited HR and T_{re} responses that were statistically similar to those of Control, hereditary heat intolerance was excluded as a causative factor in all subjects except subject A during iteration 1. The fact that subject A subsequently acclimated to exercise in the heat, at 11.5 months after heatstroke (iteration 3), suggests three things: (a) he was not hereditarily heat intolerant prior to heatstroke; (b) the concept that "one heatstroke predisposes to another heatstroke" was more likely to be true during the time that subject A was heat intolerant (29); (c) some physiological factor(s) (i.e. cardiorespiratory physical fitnes) improved to allow subject A to respond normally during heat acclimation trials.

In addition to subject A, subject E experienced difficulty completing 90 min heat acclimation trials; his trials were terminated prematurely on days 1, 2, and 4 because he displayed a final T_{re} in excess of 39.0°C. His T_{re} values decreased, however, from day 1 (39.0°C) to day 6 (38.4°C), and probably were related to his high M/SA, high body fat %, and low $\dot{V}O_2max$ (20,35,54). Also, subject E had been ordered to curtail all physical training and heat exposure, and gained 9 kg of body weight, during the 82 d which elapsed between heatstroke and testing at this laboratory.

During heat acclimation, the thermoregulatory measurements, sodium and potassium balance, and blood values for PH and Control (Tables 5, 6, 7) were statistically similar. In fact, only the measurements associated with plasma volume expansion (peak: +14.9 % for PH, +17.1 % for Control) were statistically different between days. Although sweat sensitivity, sweat rate, and sweat electrolyte losses may be altered by heat acclimation, Tables 5 and 6 demonstrate that these two factors showed no significant between-day differences during this protocol. This is not extraordinary in light of the fact that sweat gland adaptations often are not significantly altered until a minimum of 10 days of heat acclimation have been completed (4,56).

PREDISPOSING FACTORS

Dr. Epstein's review of heat intolerance, as a part of this symposium, has delineated at least 30 factors which underlie heat intolerance (19). Other authors (8,9,13,31,43,47,50) have described additional factors (i.e. differences in body fluid shifts, ethanol abuse, hypokalemia) which may predispose humans to heatstroke. Interestingly, many of these factors either have been reported in only one case report or are speculative, and differ greatly from case to case. Thus, the specific identification of physical characteristics and situational factors affecting PH at the time of exertional heatstroke is of great value in the prevention of future heatstroke casualties.

The setting in which heatstroke occurs has been classically described as one in which a dehydrated, unacclimatized, unfit individual performs strenuous exercise under severe thermal stress (34,40). Situations which existed at the time of heatstroke in PH (Table 2), did not fit this classical description, and illustrated the highly individual nature of each heatstroke case. For example, four PH experienced heatstroke during the cooler months of the year (e.g. March, October, November), the time of the day ranged from 0600h to 1000h, and dry bulb

temperatures ranged from 19 - 28°C. Exercise and high relative humidity were present in all situations (Table 2), but these two factors had been present on preceding mornings. Only subject B had not successfully completed previous training runs; during the 3 days prior to heatstroke, he stopped because of weakness and dizziness, which he attributed to a low-grade infection that had been diagnosed five weeks prior to collapse. Similarly, subjects E, I and J acknowledged that they experienced asthma, hay fever, or an upper respiratory infection prior to heatstroke; impaired respiration and medications may have altered their metabolic responses during exercise. Richards et al. (39) previously reported a high incidence of upper respiratory infection (n = 17) among 56 cases of heat exhaustion at a mass participation road race.

The Predisposing Factors Questionnaire (Table 4) indicated that sleep loss and generalized fatigue were the most common factors acknowledged by PH, during the five days prior to heatstroke. This was due either to the training or duty which PH had undertaken. Table 2 illustrates that six PH (subjects E - J) had recently begun (4 - 10 d) specialized training which involved a sudden increase in physical training, accumulated fatigue, reduced sleep (e.g. 3 - 4 h per night), and psychological stress. Khogali (32) described a series of stressful events (e.g. lack of sleep, overcrowding, noise) encountered by two million religious pilgrims which led to a relatively high incidence of heatstroke (2.3 per 1000). In one PH (subject F), transcontinental flight preceeded the beginning of specialized training, and desynchronization of circadian rhythms may have been involved (52). Subject D had slept less than 4 h during the night prior to experiencing heatstroke, because he had performed night duty. Sleep deprivation apparently has little effect on physical performance (23), but has been shown to reduce the thermosensitivity of sweating and peripheral blood flow (33), to reduce high-energy phosphate formation and serum ATP levels (37), and to double energy

expenditure in animals (42). Future investigations of these effects may clarify the mechanism by which sleep loss acts as a predisposing factor to heatstroke (32,47).

All mean physical characteristics of PH (Table 1), except body fat %, were slightly above the mean of 1170 male soldiers described by De Luca et al. (15), and all characteristics fell within $\pm$ 1 standard deviation of the mean. These PH characteristics also were not statistically different from Control. The factors which distinguished subject A from other PH and Control were: body fat %, age, $\dot{V}O_2max$ (Table 1), two previous experiences with heat exhaustion, the peak post-heatstroke CPK level (Table 3), and the number of days to each peak post-heatstroke CPK, ALT and AST levels (Table 3). Lavenne and his colleagues studied the heat tolerance of 50 Belgian mine workers in 1966 (35). They concluded that a $\dot{V}O_2max$ of 40 $ml \cdot kg^{-1} \cdot min^{-1}$ may be considered to be the boundary between "those who are able to tolerate high temperatures and those who are adversely affected." Shvartz (48) and Epstein (20) also reported low $\dot{V}O_2max$ values (41.2 and 40.0 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively) for heat intolerant P, when compared to control subjects. In close agreement with these findings, the three lowest $\dot{V}O_2max$ values ($ml \cdot kg^{-1} \cdot min^{-1}$) in the current investigation were recorded for subject A (43.74), subject E (45.73), and subject D (38.37). Interestingly, subject A was heat intolerant (iterations 1 and 2); subject E had three of his heat acclimation trials terminated (days 1, 2, and 4) because of T_{re} in excess of 39.0°F; and subject D exhibited elevated final HR and final T_{re} values during a 6-hour trial (results not shown, see methods). Eighty percent of PH were running in a group, at the time of heatstroke (Table 2). Those PH who had low $\dot{V}O_2max$ values probably experiencd above average rectal temperatures, because they were running at higher relative exercise intensities than other group members (54).

It is also prudent to consider the possibility of substrate depletion as a predisposing factor. Six PH (subjects D through I) acknowledged generalized fatigue during the five days prior to heatstroke (Table 4); five of these men experienced a dramatic increase in the volume of physical training, as they participated in specialized, high-stress training. Under these conditions, it is likely that all PH experienced markedly reduced muscle glycogen stores, because this may occur in as little as 2 - 4 h (46). Both muscle glycogen depletion (31) and hypoglycemia (13) have been proposed as factors which may predispose humans to heatstroke. Cellular energy depletion and increased reliance on anaerobic energy metabolism also have been identified as primary theoretical factors in heatstroke pathophysiology (24,25,27). It is interesting to note that PH relied on glycolytic metabolism (i.e. respiratory exchange ratio) to a significantly greater degree ($p < .025$) than Control. The effects of muscle fiber type, or selective recruitment of type 1 or type 2 fibers, on the etiology of exertional heatstroke are unknown.

Gender also may be a predisposing factor for exertional heatstroke. The 10 PH in this investigation, as well as every P described in the case reports and laboratory investigations above, were males. These facts may be explained by the following hypotheses: (1) scientific research has historically utilized male test subjects, (2) males are placed in situations which result in heatstroke more often than females, (3) males are more likely to push themselves to the point of collapse than females, and (4) males are predisposed to heatstroke because of inherent hormonal, physiological or morphological differences. Although Kumar et al. (34) reported that the incidence of non-exertional heatstroke among males was three times that of females, and attributed this to an unexplained greater susceptibility in males, gender effects deserve future research consideration.

Summary

The following statements summarize the findings of previous studies and the current investigation, regarding the time course of recovery, heat acclimation ability, and predisposing factors of P:

1. The rate of recovery from exertional heatstroke is unique to each case. At 61 $\pm$ 7 d following heatstroke, nine out of 10 PH exhibited normal heat acclimation responses, thermoregulation, whole body sodium and potassium balance, sweat gland function, and blood values. Only subject A was defined heat intolerant (at approximately two and seven months after heatstroke), but was defined heat tolerant at 11.5 months. A declaration of "clinically normal" is not always equivalent to "heat tolerant".
2. Subject A and patients with severe hepatic injury (11) demonstrate that complete recovery from exertional heatstroke may require up to one year. A primary determinant of recovery time may be the length of time between collapse and the initiation of cooling therapy (8,13,22).
3. Of the factors measured, none were clearly related to prognosis, recovery from heatstroke, or performance during heat acclimation trials. Previously described prognostic factors (47) were not valid for PH. A similar finding prompted another research team (29) to recommend that every P be examined to determine heat tolerance status.
4. All mean ($\pm$ SE) physical characteristics of PH were normal. Heat intolerant subject A was at the extreme of PH and Control data, in these factors: $\dot{V}O_2max$, age, body fat %, two previous episodes of heat exhaustion, the peak CPK level during hospitalization, and the number of days to reach peak CPK, ALT, and AST levels during hospitalization.
5. Exertional heatstroke occurred in most PH while they were running in a group at moderate exercise intensity, between 0600h - 1000h. Environmental conditions were not harsh (19 - 28^{o}C db, > 66 %rh).

6. The lowest $\dot{V}O_2max$ values (range: 38.37 - 45.73 $ml \cdot kg^{-1} \cdot min^{-1}$) were observed among the PH who performed poorly at some point in exercise-heat exposures. When running in a group, these individuals function at high relative exercise intensities and are likely to experience higher rectal temperatures than individuals with high $\dot{V}O_2max$ (54).
7. Unexpected, large serum CPK elevations (range: 838 - 5625 $U \cdot l^{-1}$) were observed in three PH (group P2) during heat acclimation trials. Although these elevations may have been sequela of heatstroke (i.e. abnormal membrane permeability), evidence supports the hypothesis that they were due to the eccentric nature of one exercise trial (38) and the inactive status of group P2 prior to testing. Subsequent iterations of this protocol revealed a trend toward normal serum CPK levels in these three PH.
8. Many factors predispose humans to exertional heatstroke. The situations of PH (Tables 2, 4) emphasized that the coincidental introduction of multiple stressors (e.g. sleep loss, sudden increase in physical training, lengthy exposure to heat stress) is critical.
9. Heat intolerance (i.e. an inability to adapt to exercise in a hot environment) occurs in a small percentage of P. This phenomenon may be temporary (29) or permanent (20,45,48). In the etiology of exertional heatstroke, the importance of situational factors is highlighted by the fact that none of the 10 PH in this investigation were hereditarily heat intolerant.

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NOTE:
The following references contain four (4) references which were a part of this symposium (ACSM National Convention, Session A-1, 31 May 1989, "Exertional Heatstroke: An International Perspective"), and therefore are incomplete. Editor may complete these references, when volume, page and date are known.

These references are numbered: 12, 19, 24, 44, by Epstein, Hubbard, Shapiro and Costrini.

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Figure Titles

FIGURE	TITLE
1	Schedule of testing and measurements for PH and Control.
2	Mean ($\pm$ SE) final HR values on day 1 and day 6 of 90 min heat acclimation trials. Symbols: closed circle - heat intolerant subject A, closed bars - PH (n = 9), shaded bars - Control (n = 5). Significant differences ($p < .05$) existed beween day 1 and day 6 values, for PH and Control.
3	Mean ($\pm$ SE) final T_{re} values on day 1 and day 6 of 90 min heat acclimation trials. Symbols are identical to those in Figure 2. Significant differences existed between day 1 and day 6 values, for PH ($p < .01$) and Control ($p < .025$).
4	Pre-exercise serum CPK values (mean $\pm$ SE) of groups P1 (n = 7), P2 (n = 3), and Control (n = 5). Groups P1 and P2 were subsamples of PH, separated for the purpose of serum enzyme analysis (see results). Arrow denotes the upper level of the normal range. Significant differences ($p < .01$) existed between P2 and P1 (day 1), and between P2 and Control (day 1).

(continued)

Figure Titles (cont.)

FIGURE	TITLE
5	Pre-exercise serum LDH values of groups P1, P2, and Control. Symbols are identical to those in Figure 4. Significant differences ($p < .01$) existed between P2 and P1 (day 1), and between P2 and Control (day 1).
6	Pre-exercise serum AST values of groups P1, P2, and Control. Symbols are identical to those in Figure 4. Significant differences ($p < .01$) existed between P2 and P1 (B, day 1), and between P2 and Control (day 1).
7	Pre-exercise serum ALT values of groups P1, P2, and Control. Symbols are identical to those in Figure 4. Significant differences ($p < .05$) existed between P2 and P1 (B, day 1, day 4), and between P2 and Control (B, day 1, day 4).
8	Pre-exercise serum CPK, LDH, AST, and ALT values of subject F, during three iterations of this protocol (40 d, 4 months, and 8 months after heatstroke, respectively). Subject F was a member of group P2 in figures 4 - 7. Arrows denote the upper level of the normal range for each enzyme.

TABLE 1. Selected characteristics of PH.

	Age (yr)	Height (cm)	Body mass (kg)	Surface area (m^2)	M/SA ($kg \cdot m^{-2}$)	Body fat (%)	$\dot{V}O_2max$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	Number of Days Post-heatstroke (Initial Testing)
A	44	175	82.420	1.98	41.6	22.4	43.74	56
B	22	182	84.470	2.06	41.0	19.5	53.09	46
C	21	189	79.060	2.06	38.4	10.0	59.85	25
D	24	188	96.010	2.23	43.1	17.9	38.37	69
E	22	168	88.140	1.98	44.5	24.6	45.73	82
F	24	193	97.230	2.22	43.8	18.6	47.31	40
G	26	188	93.590	2.20	42.5	16.8	51.92	48
H	26	175	68.680	1.83	37.5	14.6	58.14	76
I	26	176	85.750	2.02	42.4	17.3	50.59	99
J	24	167	78.890	1.88	42.0	14.3	50.56	67
mean	26	180	85.420	2.05	41.7	17.6	49.93	61
± SE	2	3	2.790	.04	0.7	1.3	2.05	7

TABLE 2. Situational factors present at the time heatstroke occurred.

Subject	Time of day	Ambient conditions *		Exercise factors			Clothing Worn	Undergoing specialized training? **
		db temp. (^{o}C)	Relative humidity (%)	Type of activity	Estimated speed of run ($km \cdot h^{-1}$)	Distance completed (km)		
A	0700	23	--	PT	12.1	4.8	T	NO
B	0600	25	97	PT	12.1	8.9	T	NO
C	1000	23	66	CF	15.3	10.0	T	NO
D	0600	22	98	PT	12.1	7.2	--	NO
E	0600	19	96	PT	12.1	6.4	B	YES
F	0900	28	85	PT	12.1	7.2	B	YES
G	0630	23	86	PT	12.1	4.8	B	YES
H	0630	23	86	PT	12.1	4.8	B	YES
I	0700	19	--	PT	13.8	4.8	B	YES
J	1000	--	--	CF	13.8	8.1	T	YES

Abbreviations: db temp. - dry bulb temperature; PT - group physical training run; CF - competitive footrace; T - wore t-shirt, shorts, socks, sneakers and undershorts; B - wore t-shirt, cotton trousers, socks, sneakers and undershorts.

* - official meterological records

** - involved special military training, such as Basic/Airborne/Ranger Training

TABLE 3. Characteristics of PH during heatstroke and hospitalization.

Subject	Maximal T_{re} (°C)*	Spontaneous cooling?	Mental status and duration (h)	Peak post-heatstroke serum enzyme levels ** CPK (units·l^{-1})	LDH (units·l^{-1})	AST (units·l^{-1})	ALT (units·l^{-1})
A	40.0	no	disoriented (---)	18,120 (5)	500 (4)	281 (5)	196 (3)
B	41.1	no	coma (7.5)	---	***	***	---
C	41.1	no	coma (0.4)	263 (1)	294 (1)	351 (3)	221 (5)
D	41.1	no	disoriented (0.3)	327 (2)	821 (2)	4,680 (2)	---
E	41.1	no	disoriented (1.0)	1,703 (1)	405 (1)	149 (2)	148 (2)
F	41.1	---	disoriented (5.0)	1,928 (1)	406 (1)	111 (4)	202 (5)
G	41.1	---	coma (0.4)	3,820 (1)	---	206 (2)	210 (3)
H	41.8	no	coma (---)	7,480 (1)	522 (1)	284 (2)	407 (2)
I	41.1	---	coma (0.1)	3,182 (1)	260 (1)	---	88 (1)
J	40.4	no	disoriented (0.2)	14,160 (2)	1,390 (2)	1,200 (2)	2,145 (3)
mean	41.0			5,664	575	908	452
± SE	±0.2			± 2,133	± 132	± 553	± 294

* - All measurements were taken in the field, except patient J (emergency room). Some rectal thermometers read only to 41.1°C.

** - Number of days to reach maximal level is shown in parentheses. Normal enzyme concentration ranges are: CPK - 33-213 units·l^{-1}, LDH - 92-186 units·l^{-1}, AST - 7-32 units·l^{-1}, ALT - 2-45 units·l^{-1}.

*** - Serum enzyme measurements were made on post-heatstroke day 4 only, as follows: LDH - 865 units·l^{-1}, AST - 490 units·l^{-1}.

TABLE 4. Results of Predisposing Factors Questionaire administered at initial meeting with PH.

Predisposing factor or warning signal	Number of PH who acknowledged this factor (n = 10) *
sleep loss	7
generalized fatigue	6
a warning sign of impending illness	6
a long exercise bout or workout	5
a long heat exposure (e.g. mowing grass, physical training)	5
a heat wave	4
reduced sweat secretion	3
fever or disease	3
dizzy, light-headed	2
dehydration	1
taking medication (i.e. antihistamine)	1
excessive use of alcohol	1
excessive use of caffeine	1
consumption of a low salt diet	1
previous heat illness	1
sunburn or skin rash	1
immunization or innoculation	0
use of diuretics	0
previous difficulty with exercise in the heat	0
diarrhea or vomiting	0

* - during the five days prior to heatstroke episode

TABLE 5. Selected thermoregulatory measurements (mean ± SE) at end of 90 min heat acclimation trials on days 1 and 6. No between-group or between-day significant differences were observed in these values.

Measurement (unit)	PH (n = 9)		Control (n = 5)	
	day 1	day 6	day 1	day 6
$\bar{T}_{sk}$ (^{o}C)	35.50 ± 0.23	35.20 ± 0.24	35.84 ± 0.35	35.45 ± 0.22
heat storage ($kcal \cdot m^{-2} \cdot h^{-1}$)	33.0 ± 3.5	25.7 ± 3.5	34.3 ± 1.9	25.7 ± 3.0
$T_{re} - \bar{T}_{sk}$ (^{o}C)	3.14 ± 0.24	2.93 ± 0.22	2.75 ± 0.28	2.73 ± 0.23
HASG ($glands \cdot cm^{-2}$)	53 ± 5	---	54 ± 2	---
sweat rate ($g \cdot m^{-2} \cdot h^{-1}$)	490 ± 40	530 ± 20	480 ± 50	490 ± 30
sweat sensitivity ($g \cdot m^{-2} \cdot h^{-1} \cdot {}^{o}C^{-1}$)	370 ± 40	470 ± 60	360 ± 60	450 ± 90

TABLE 6. Mean (± SE) sodium and potassium balance (total mEq·24 h^{-1}) of PH and Control during heat acclimation.

Subject group	n	Electrolyte	Source of electrolyte loss	Day of 90 min trials			Mean 24 h ad libitum consumption	Mean 24 h electrolyte balance
				day 1	day 4	day 7		
PH	9	sodium	urine	70	109	145		
			sweat	62	67	68		
			total body*	139	183	220	179 ± 12	0 ± 22
Control	5		urine	97	136	107		
			sweat	86	66	75		
			total body*	190	209	189	166 ± 25	-30 ± 20
PH	9	potassium	urine	73	58	67		
			sweat	8	10	9		
			total body*	92	79	87	94 ± 5	8 ± 6
Control	5		urine	66	95	78		
			sweat	11	9	11		
			total body*	88	115	100	85 ± 8	-16 ± 11

* - corrected for estimated fecal loss of 7 mEq Na^+·24 h^{-1} and 11 mEq K^+·24 h^{-1} (ref. 36)

TABLE 7. Mean (±SE) pre-exercise blood values of PH and Control on B, day 4, and day 7 of heat acclimation trials.

Measurement (unit)	PH (n = 9)			Control (n = 5)			Statistical significance
	B	day 4	day 7	B	day 4	day 7	
hematocrit (%)	50.2 ± 1.2	46.2 ± 0.5	47.0 ± 1.0	50.0 ± 1.0	44.7 ± 1.4	45.7 ± 1.2	.025 *
hemoglobin ($g \cdot dl^{-1}$)	16.7 ± 0.4	15.5 ± 0.2	15.6 ± 0.4	16.2 ± 0.4	15.0 ± 0.4	14.8 ± 0.3	.05**, .05***
MCHC ($g \cdot dl\ rbc^{-1}$)	33.3 ± 0.1	33.5 ± 0.1	33.2 ± 0.1	33.2 ± 0.1	33.6 ± 0.1	32.5 ± 0.1	NS
Δ PV (%)		+[illegible] ± 2.9	+10.1 ± 3.4		+17.1 ± 3.1	+17.2 ± 3.6	NS
total protein ($g \cdot dl^{-1}$)	7.3 ± 0.2	6.8 ± 0.2	7.0 ± 0.1	7.6 ± 0.5	7.5 ± 0.3	7.6 ± 0.3	NS
plasma sodium ($mEq \cdot l^{-1}$)	142 ± 1	142 ± 1	141 ± 1	143 ± 1	142 ± 2	142 ± 1	NS
plasma potassium ($mEq \cdot l^{-1}$)	4.2 ± 0.1	4.2 ± 0.1	4.2 ± 0.1	4.6 ± 0.2	4.4 ± 0.1	4.4 ± 0.1	NS
plasma osmolality ($mOsm \cdot kg^{-1}$)	287 ± 1	286 ± 2	289 ± 1	289 ± 3	287 ± 2	286 ± 1	NS

* - from baseline to day 4 in PH and Control

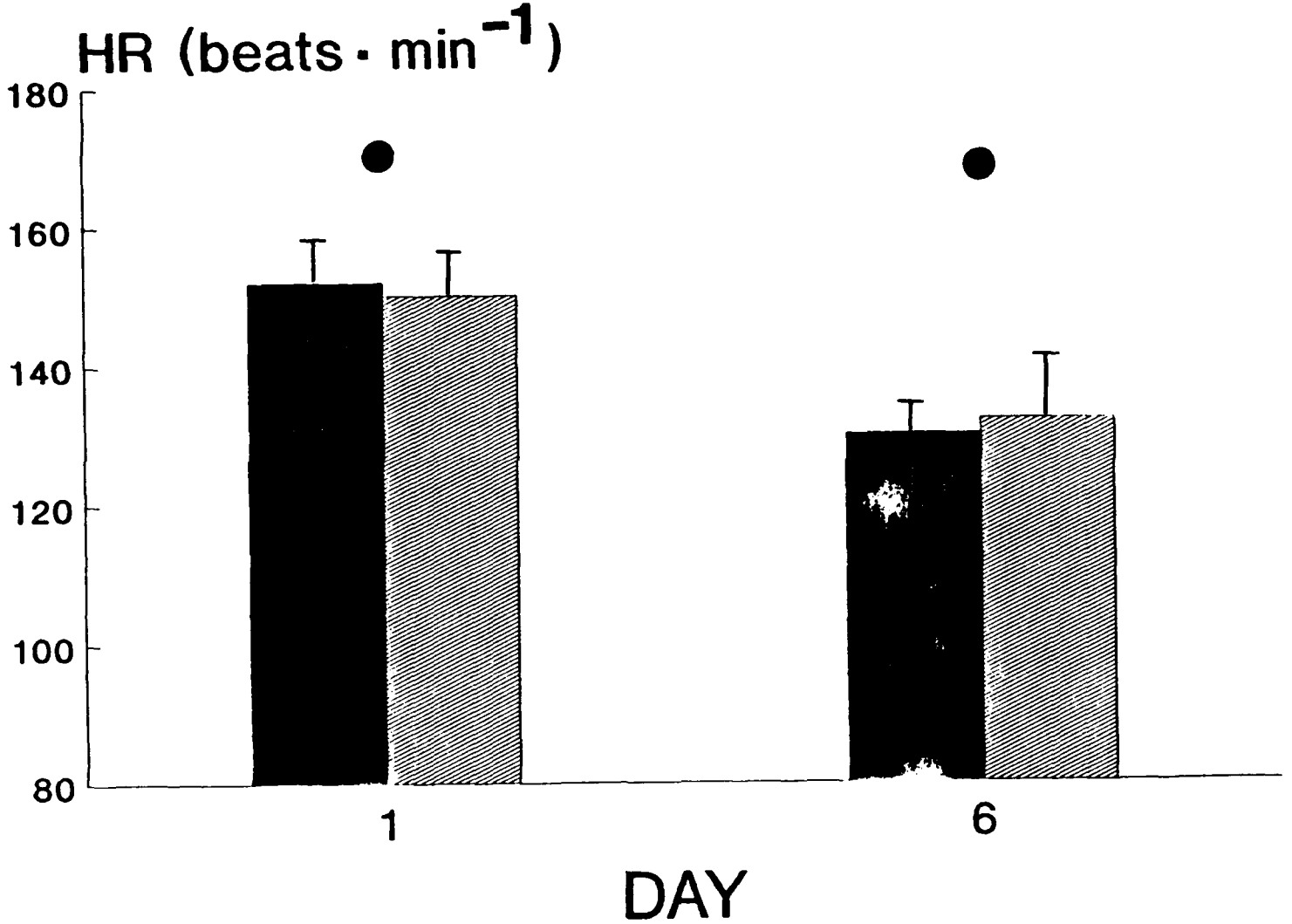
** - from baseline to day 4 in PH only

*** - from baseline to day 7 in PH only

FIGURE 1

EVENT	DAY OF INVESTIGATION								
	B	1	2	3	4	5	6	7	Post
90 min acclimation trial		X	X	X	X	X	X	X	
Anthropometric indices	X								
Entering body mass	X	X	X	X	X	X	X	X	
Dietary record	X	X	X	X	X	X	X	X	
T_{re}, T_{sk}, HR, RPE		X	X	X	X	X	X	X	
Sweat rate		X	X	X	X	X	X	X	
$\dot{V}O_2$ submax		X							
$\dot{V}O_2$ max									X
Blood sample	X				X			X	
HASG		X							
Whole body washdown		X			X			X	
Urine volume, electrolytes, specific gravity	X	X	X	X	X	X	X	X	

FIGURE 2



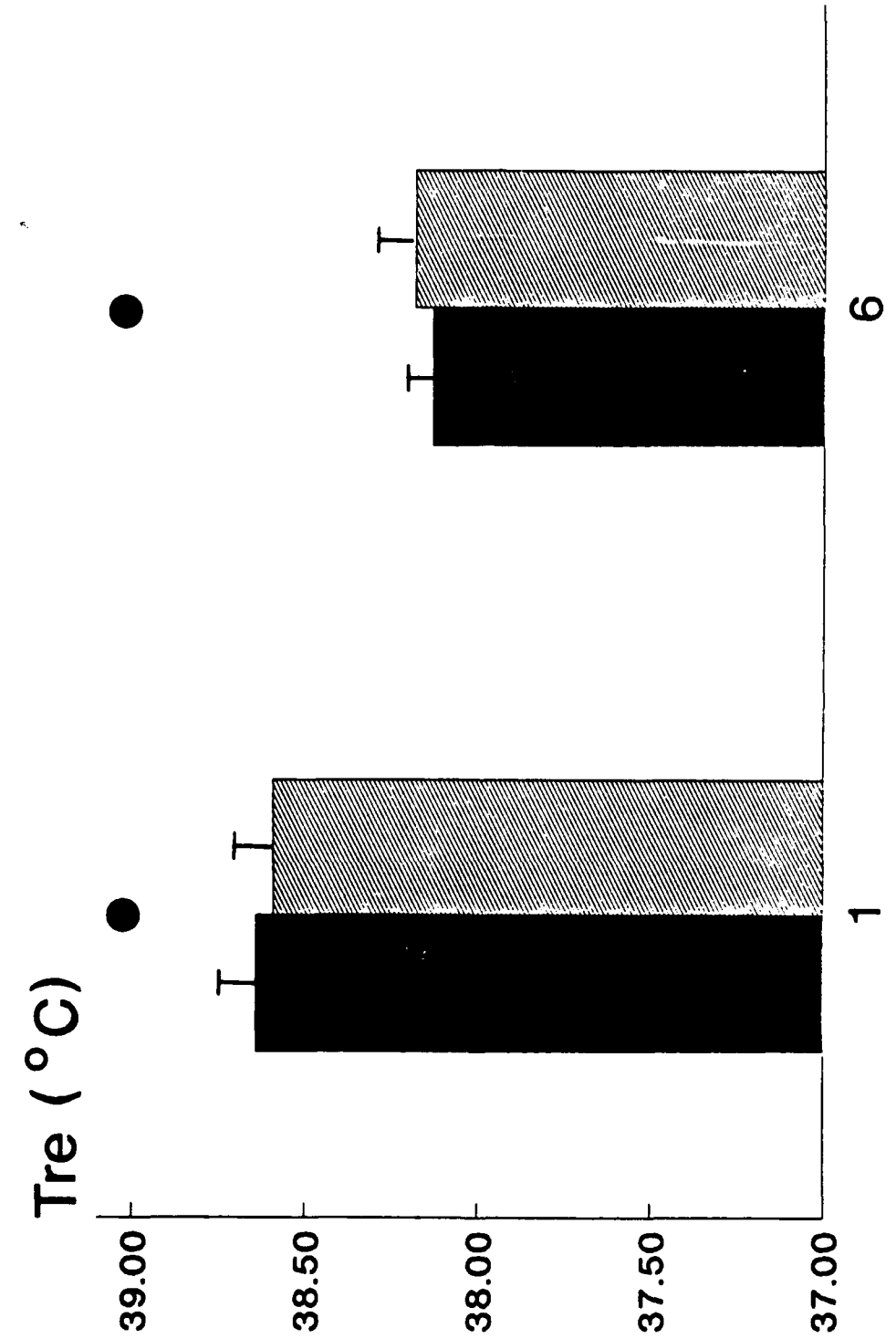
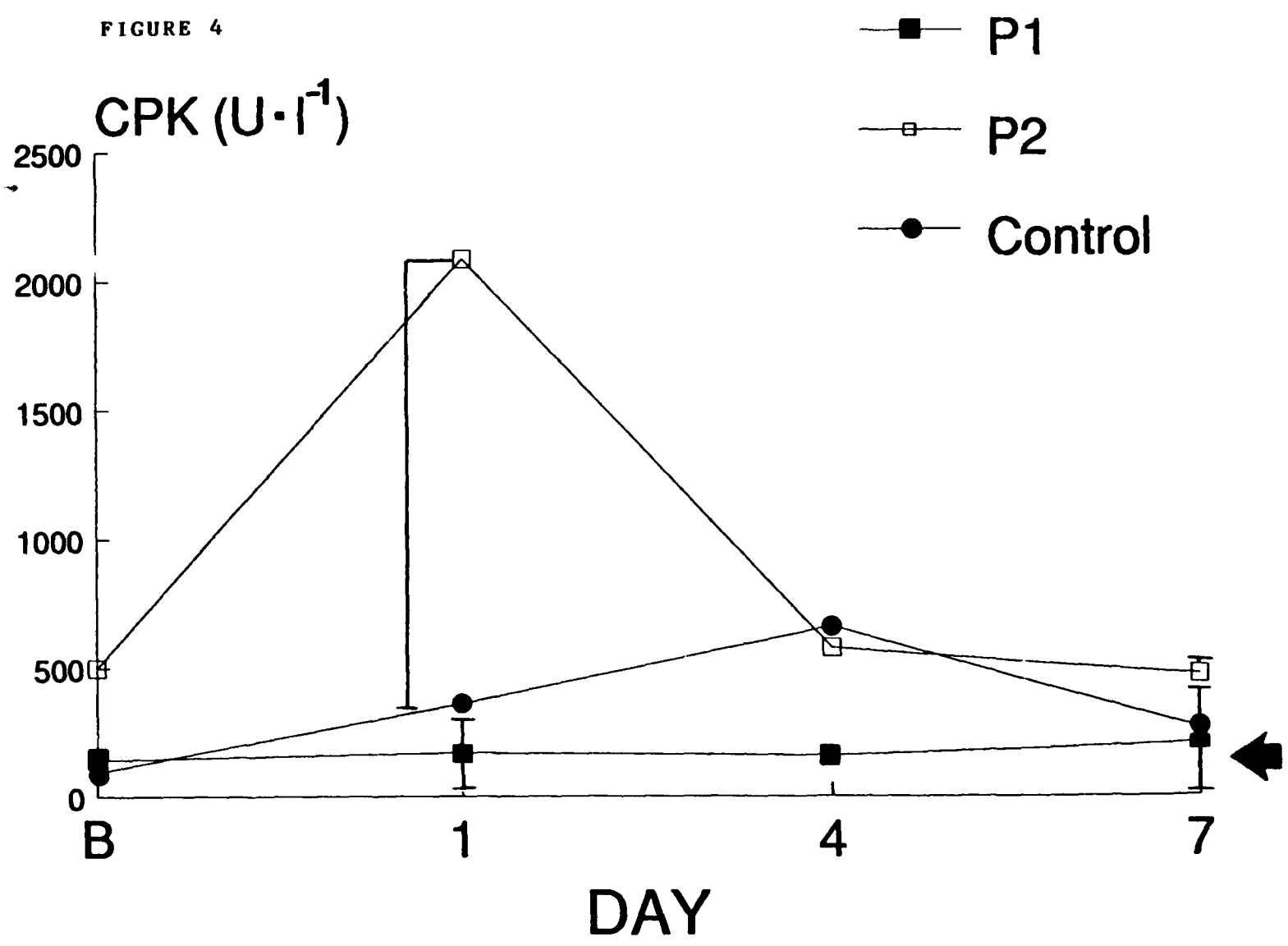


FIGURE 3

FIGURE 4



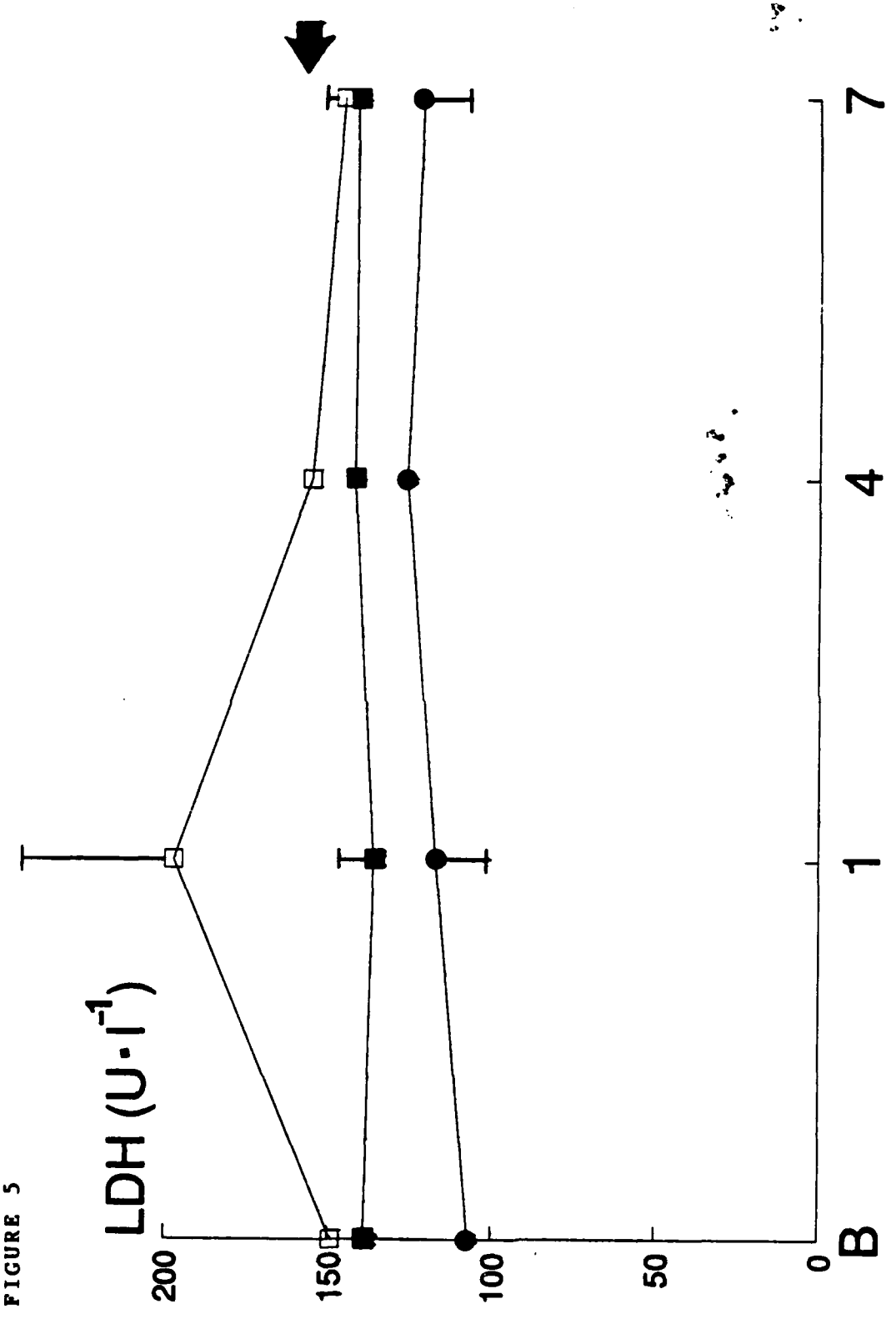


FIGURE 5

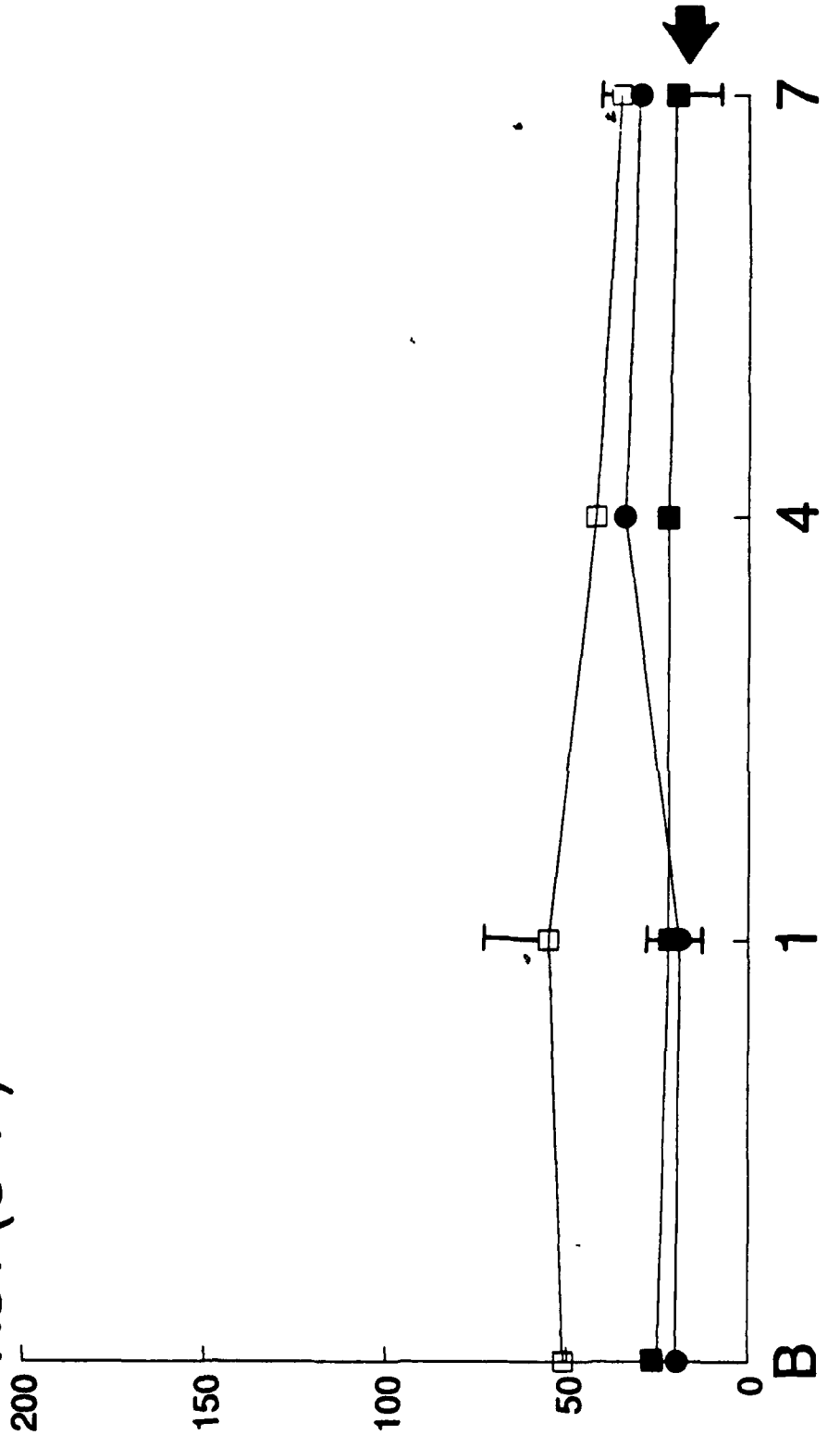


FIGURE 6

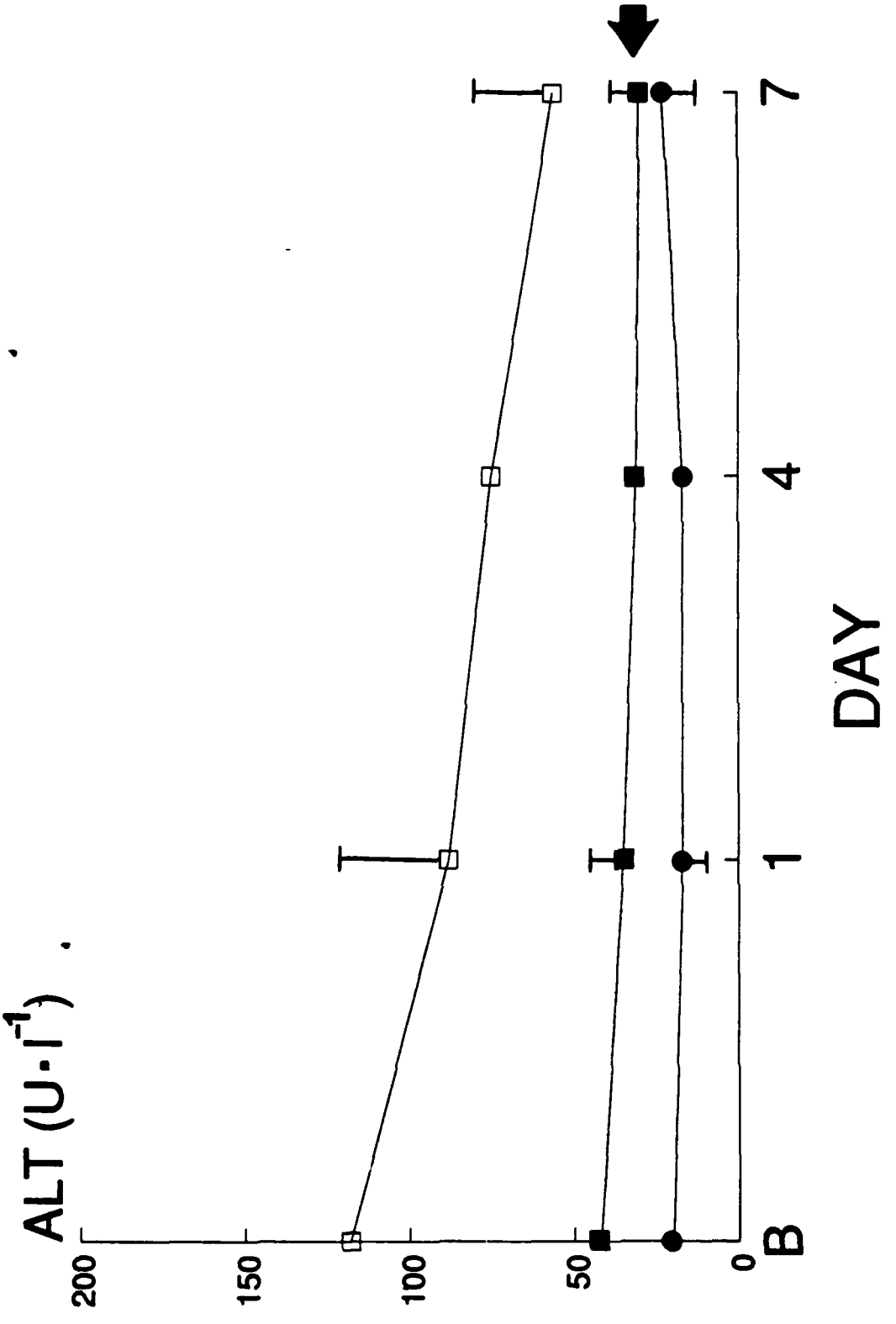
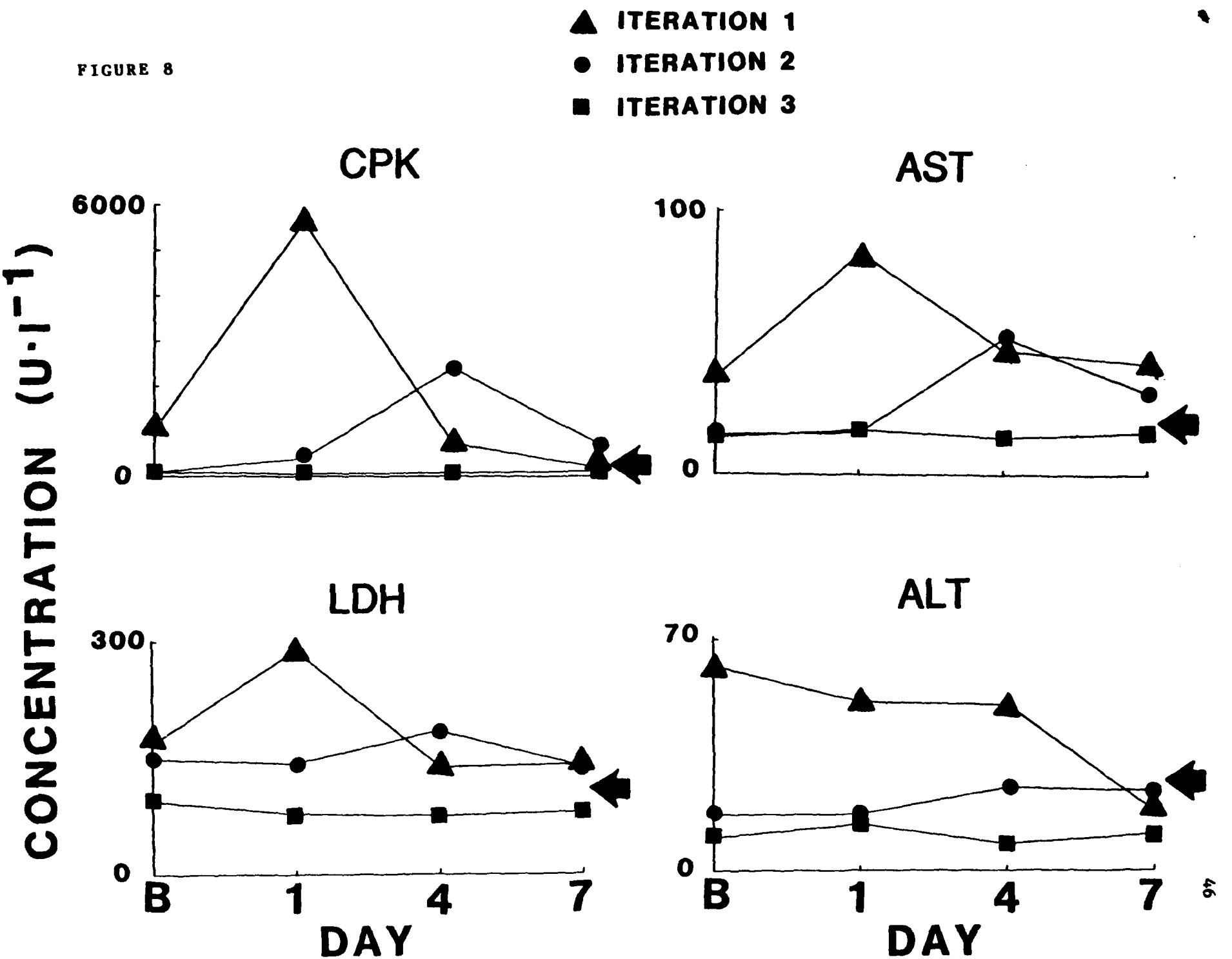


FIGURE 7

FIGURE 8


ITERATION 1
ITERATION 2
ITERATION 3
CPK
AST
LDH
ALT
6000
0
100
0
300
0
70
0
CONCENTRATION (U·l⁻¹)
B
1
4
7
DAY
B
1
4
7
DAY