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The Effect of Exercise on 1 mcg ACTH Stimulation of the Hypothalamic-Pituitary-Adrenal Axis

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Abstract

The Low Dose (1 µg) ACTH Stimulation Test (LDST) is useful in the evaluation of the Hypothalamic-Pituitary-Adrenal (HPA) axis. The effect of physiological stressors on its accuracy is not known. We examined the effect of prior exercise on the assessment of the HPA axis with the low dose ACTH stimulation test.

Twenty-six healthy male subjects had baseline cortisol levels drawn at two-hour intervals on the initial day of the study. On day two, the LDST was performed at rest. On day three, subjects exercised by completing stage I-V of a Bruce treadmill protocol, followed by the LDST after one hour of rest. We found that mean peak cortisol levels at 30 and 60 minutes after the LDST did not differ between the day of exercise and the day of rest. The mean maximal change in cortisol levels at 30 and 60 minutes also did not differ. However, mean baseline cortisol levels before exercise began were higher on the day of exercise than on the rest day ($p<0.001$). Mean ACTH levels at these times were not significantly different ($p=0.09$).

The adrenal response to a LDST test is not affected by prior physiologic stress in the form of exercise in non-sedentary adult males.

Keywords: Adrenal insufficiency; Physiologic stress; Cortisol; Cosyntropin

Introduction

The low dose (1 µg) Adreno-Cortico Tropic Harmone (ACTH) stimulation test (LDST) is useful in the evaluation of the hypothalamic-Pituitary-Adrenal (HPA) axis. Proposed uses of the LDST include assessment of secondary adrenal insufficiency in the outpatient or critical care setting [1,2]. The appealing characteristic of the LDST is that it produces lower cortisol elevations than the Standard Dose (250 µg) ACTH Stimulation Test (SDST) which may make it a more sensitive test in mild disease [3-11]. Given that the LDST produces smaller elevations in serum cortisol, a number of variables which have not been fully elucidated may affect its accuracy.

Exercise is one of the known stimulators of the HPA axis. Recognized factors that can affect the extent of HPA stimulation in relation to exercise include timing of prior meals, gender, ethnicity, body composition, and athletic fitness level [12-16]. Exercise of sufficient intensity and duration may produce a different response to HPA axis testing [17-19]. The physiologic mechanisms of this process have not been fully elucidated. Whether or not exercise influences testing of the HPA axis has not been established. This study's objective was to investigate the effect of exercise in healthy male subjects on the LDST. Establishing the impact of exercise on the LDST would assist in determining its applicability in different patient populations and clinical settings.

Methods

Subjects

Twenty-six healthy men volunteered for the study after giving informed consent. They were each interviewed and examined by a physician and excluded if they had significant current illness, past medical problems, family history or medications which were known to interfere with the HPA axis. Specifically, subjects with airway disease, reliance on steroid preparations, or a history consistent with an abnormal cardiac or pulmonary process were excluded from the study. Prior exercise histories were taken to estimate level of conditioning of each subject. Subjects received specific instructions to eat three full meals in the 24 hours the day prior to and on each day of the study. They were also instructed to obtain at least 7 hours of sleep the night prior to testing. Each subject signed a consent form to voluntarily participate in the study. The protocol was reviewed and approved by the Investigational Review Board at the National Naval Medical Center in Bethesda, Maryland.

Method of ACTH preparation

A 250 µg vial of synthetic ACTH or cosyntropin (Cortrosyn; Organon, Inc., West Orange, New Jersey) was mixed with 2.5 mL of 0.9% sterile normal saline solution. Each vial was diluted in 250 mL of 0.9% normal saline creating a concentration of 1 µg/ml of cosyntropin.

Testing day 1

Subjects reported to the laboratory at 0800 h. Serum cortisol levels were drawn at two-hour intervals for a total of five blood samples. They were allowed to return to work between blood draws and instructed to continue with routine work related activities.

Testing day 2

Subjects reported to the laboratory at 1300 h. Vital signs were obtained and reviewed by a physician. Each subject then received a heparin lock intravenous catheter in an antecubital vein. After baseline blood samples for ACTH and cortisol were obtained, 1.0 mL of the 1 µg/

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ml cosyntropin solution was injected intravenously. Subjects remained in a seated, resting position during this phase of testing. Serum cortisol levels were obtained at 30 and 60 minutes after injection in accordance with standard testing as recommended by the manufacturer. Subjects were then monitored for a one hour period after testing was complete.

Testing day 3

Subjects reported to the laboratory at 1300 h. An electrocardiogram and baseline vital signs were obtained and reviewed by a physician. An intravenous catheter was placed and blood ACTH and cortisol levels were collected. Subjects were then asked to exercise on a treadmill following stages I-V of a standard Bruce protocol [20]. In this protocol, subjects exercise for five intervals of three minutes starting at a speed of 1.75 mph and 10% grade. The maximum treadmill speed in the protocol is 5.0 mph with an 18% grade. Although subjects were encouraged to complete the session, the test was terminated at the discretion of the monitoring physician or if subjects requested to stop. After cessation of exercise, subjects were allowed to rest. After one hour of rest, serum samples were drawn for post-exercise ACTH and cortisol levels. Subjects were then given 1.0 ml of the 1 μg/ml cosyntropin solution intravenously. Serum cortisol levels were obtained again at 30 and 60 minutes post injection.

These testing days were consecutive days. Testing occurred for 10 hours on test day 1, one hour on test day 2, and four hours on test day 3. 19 hours occurred between the last blood draw on testing day one and the first blood draw on test day 2. Between test day 2 and test day 3, 24 hours occurred between the blood draws.

Run	68.6 ± 78.0
Walk	109.0 ± 127.9
Basketball	25.4 ± 56.8
Swim	15.0 ± 26.9
Cycle	32.7 ± 58.8
Other	65.7 ± 109.9
Total*	316.3 ± 276.0

Values are means ± S.D.

Table 1: Exercise histories given by subjects Length of exercise, minutes per week.

Processing of blood samples

All cortisol and ACTH samples collected were immediately stored at -20°C and processed together at the study's completion. Cortisol determinations were obtained using the Abbott AxSYM System (Abbott Laboratories, Abbott Park, IL). This assay utilizes Flourescence Polarization Immunoassay (FPIA) for the quantitative measurement of cortisol in human serum. ACTH samples were processed by automated competitive chemiluminescent immunoassay (Quest Diagnostics Nichols Institute, Chantilly, VA).

Statistical analysis

The student's t test was used to calculate P values and compare means. $P<0.05$ were considered statistically significant.

Results

The mean subject age was 33.2 ± 6.4 years; range 23-51. Mean total weekly aerobic exercise was 8.5 ± 6.3 sessions. The mean duration was 316.3 minutes with a range of 20-1170 minutes (Table 1).

The mean baseline ACTH level on day 1 was 18.2 ± 14.7 pg/ml**.** On subsequent days 2 and 3, the mean baseline ACTH levels did not differ significantly ($p=0.09$). The value on day 2 was 12.4 ± 10.0 pg/ml and on day 3 it was 15.0 ± 10.5 pg/ml.

As graphed in Figure 1, the mean cortisol levels on day 1 collected at two-hour intervals were as follows: 0800 h, 15.3 ± 4.3 μg/dL; 1000 h, 10.4 ± 3.6 μg/dL; 1200 h, 9.0 ± 3.7 μg/dL; 1400 h, 8.8 ± 3.4 μg/dL; 1600 h, 6.9 ± 3.1 μg/dL.

The mean baseline cortisol level on day 2 was 8.7 ± 3.5 μg/ml. In comparison, on day 3 the baseline cortisol was significantly greater at 11.0 ± 3.2 μg/mL, $p=0.01$. One hour post exercise on day 3, the serum cortisol was lower than the baseline level at 7.9 ± 2.6 μg/dL; $p<0.001$.

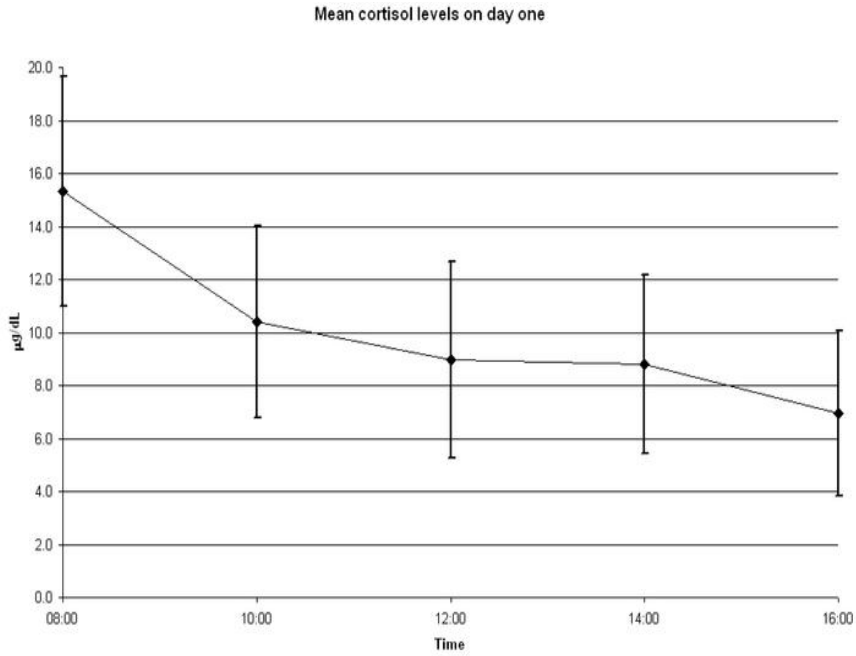

Figure 1: Serial mean cortisol levels drawn at two hour intervals on testing day 1, at rest, Values are mean ± SD.

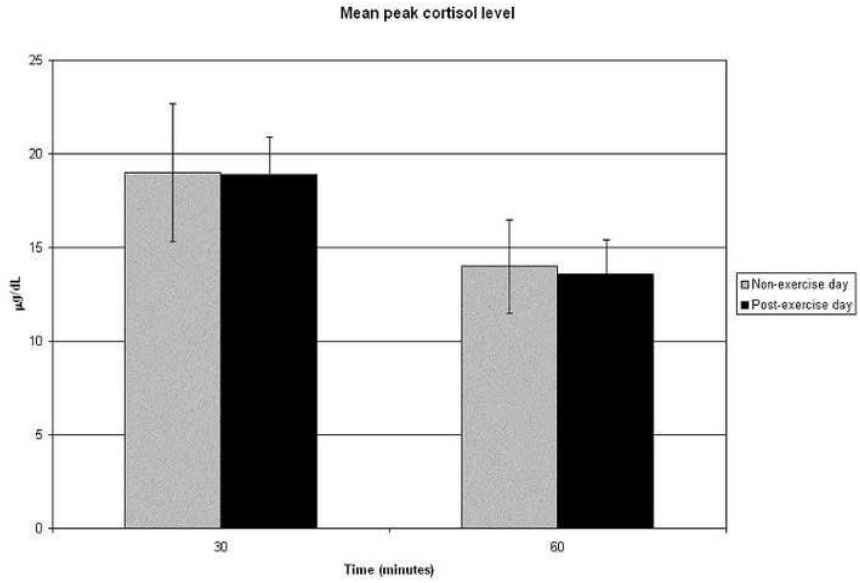

Figure 2: Mean peak cortisol levels at 30 and 60 minutes after the LDST on day two (non-exercise day) and day three (post-exercise day) of testing Values are mean ± SD.

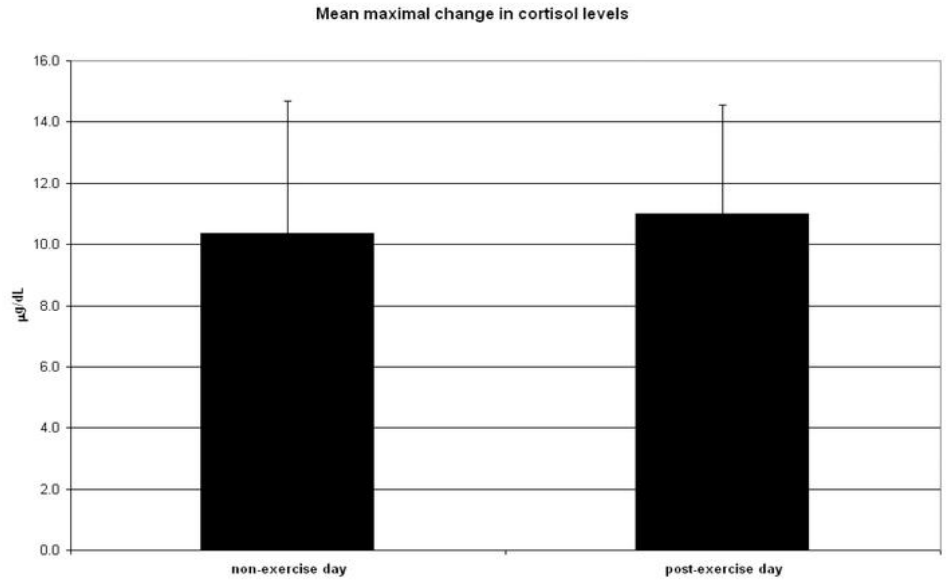

Figure 3: Mean maximal change in cortisol levels from baseline on day two (non-exercise day) and day three (post-exercise day) of testing; Values are mean ± SD.

Mean peak cortisol levels at 30 and 60 minutes after the LDST are graphed in Figure 2. The mean peak cortisol level at 30 minutes after 1 µg ACTH stimulation on day 2 was 19.0 ± 3.7 µg/dL. This did not differ significantly between the mean peak cortisol levels of 18.9 ± 2.5 µg/dL at 30 minutes after 1 µg of ACTH stimulation on day 3. At 60 minutes, the mean peak cortisol levels also did not differ between day 2 (14.0 ± 2.0 µg/dL) and 3 (13.6 ± 1.8 µg/dL).

Figure 3 shows that the mean maximal change in cortisol levels from zero to 30 minutes as well as from 30 to 60 minutes after 1 µg ACTH stimulation did not differ between day 2 (10.4 ± 4.3 µg/dL) and day 3 (11.0 ± 3.6 µg/dL; p=0.48).

Discussion

The LDST produces lower elevations in serum cortisol compared to the SDST and is thus affected to a greater degree by many variables. In this study, we have shown that prior exercise in healthy, active, adult males has no effect on peak cortisol or maximal change in cortisol achieved with the LDST.

This study implies that individuals undergoing the LDST may exercise on the day of the test. In our study, subjects reported exercise histories with a mean total weekly duration of 316.3 minutes but a wide range of variability in activity was observed. A quantitative

determination of athlete fitness level was not performed but guidelines for exercise provided by the American College of Sports Medicine suggest our subjects who were all active duty officers in the United States Navy were in the mild to moderate fitness range [21]. It is precisely this type of subjects who are exercising regularly in a variety of activities who would be most likely to have exercised on the day of a planned test. The Bruce protocol was used to simulate routine exercise because it the commonly used measure of exercise capacity in clinical practice. Various societies such as the American Heart Association have advocated its use as a standard test that is inexpensive, easy to administer, and safe [22]. While we did not aim to standardize exercise capacity, the treadmill has been shown to be a reasonably accurate method of estimating exercise capacity compared to direct measures such as maximal oxygen uptake [23]. In this study we chose to examine whether prior exercise would affect the LDST and by using the Bruce protocol have made it more applicable to an average patient.

When the LDST was performed, a mean post-exercise cortisol peak at both 30 and 60 minutes was not statistically different from levels drawn after the test on a day of rest. Duclos et al. [5] found that serum cortisol levels were significantly elevated after two hours of rest following vigorous exercise above levels drawn at rest. Despite increased baseline values, these authors did not find any difference between peak cortisol levels after the SDST was performed. Luger et al. [15] found that cortisol levels remained below 10 μg/dL in untrained, moderately trained or highly trained endurance athletes 60 minutes post exercise at 50% of maximal oxygen consumption. However, when the same individuals were exercised at 70 and 90% of maximal oxygen concentration, they had proportional elevations in ACTH and cortisol levels which remained elevated at 60 minutes. This group did not find a significant difference in degree of cortisol elevations between their study's groups of untrained, moderately trained or highly trained endurance athletes after exercise [15]. In marathon runners who were made to run on a treadmill until exhaustion, higher cortisol levels were sustained 120 minutes post exercise [24]. In another study in which moderately fit young men were exercised on a treadmill at gradually increasing speeds for 30 minutes to target a VO_2 max <4.0 mmol/liter, cortisol levels remained elevated above a baseline for 150-155 minutes [25]. The intensity and duration of exercise remains a variable in the degree of stimulation of the HPA axis.

Mean baseline ACTH levels did not differ between non-exercise and exercise days, but mean baseline cortisol levels were higher on day of exercise. Luger et al. [15] noted an elevation in baseline ACTH levels and cortisol levels in highly trained athletes. These authors concluded that there was a basal hypercortisolism in highly trained athletes which did not exist in untrained athletes. However, our study demonstrates that there is an isolated elevation in basal cortisol levels on the day of exercise which did not occur on the day of rest. Anticipation of exercise has been shown to cause an increase in serum cortisol, which may dampen with sustained physical conditioning [26].

Lack of precision and accuracy of measurement and administration of a 1μg Cosyntropin dose remain known limitations and disadvantages of the LDST and might explain the lack of differences or the modest stimulation observed. Nevertheless, the technique of measurement and batch processing of all samples were a standardized and controlled part of our protocol suggesting a consistent source of error, if any.

Additional limitations to this study include a lack of control for subject sleeping patterns and psychological stressors which certainly do affect the HPA axis. We also did not control meal intake prior to testing. Exercising after a meal can dampen the cortisol surge that exercise induces [12,27]. Timing of exercise also could have played a role in our findings. Kanaley et al. [25] found that peak cortisol concentrations in response to exercise were significantly greater at 0700 compared to 1900 and 2400. We chose for our subjects to exercise in the early afternoon precisely in order to avoid the confounding effects of hormonal diurnal variations. Also, since our study was limited to males only, it is unknown whether these findings can be generalized to females.

In this study we have shown that prior exercise in healthy, active, adult males has no effect on the accuracy of the LDST. To our knowledge, this is the first study to demonstrate the utility of the LDST in post exercise conditions. Further research is warranted to examine whether other variables such as psychological stressors may affect the LDST.

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