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EFFECTS OF TWO KINDS OF EXHAUSTIVE MAXIMAL EXERCISE ON PRO-INFLAMMATORY CYTOKINES CONCENTRATIONS IN TRAINED AND UNTRAINED HUMANS

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Abstract. The aim of this work is to identify the effect of maximal physical exercise on pro-inflammatory cytokines serum concentrations. The study has been carried on 7 endurance-trained athletes, 7 resistance-trained athletes, and 7 untrained subjects. Each subject has undergone two track races up to exhaustion. The first race is a continuous incremental event (VAMEVAL test), the second one is also continuous but with a constant intensity (Time-Limited test). Two blood samples were taken after each test, at rest and immediately after the effort. Results have shown many effects of maximal physical exercise on pro-inflammatory cytokines concentrations. Indeed, IL-1β level increased significantly in all groups under the two tests (p=0.018 for al.). The untrained subjects had the lowest concentrations but differences were not statistically significant, and endurance-trained athletes values were more important after the Time-Limited test (p=0.017). Significant increase in circulating IL-6 was also noted after the two events in all subjects (p=0.018). A substantial superiority, in favor of untrained subjects was observed after the incremental event (p=0.017); and no differences were found between athletes. Data were more important after the Time-Limited test at untrained subjects (p=0.028), and at resistance-trained athletes (p=0.018). A substantial correlation between the IL-6 concentration and maximal aerobic speed was observed after the constant intensity exercise test (r=-0.487; p=0.025). A significant changes in TNFα serum concentrations were also found after the two exercise tests in all groups (p=0.018). A significantly differences were noted between endurance-trained athletes and the other two groups (p=0.018 for al.); and no differences were found between resistance-trained athletes and the untrained subjects. In the end of the incremental event, a significant correlation was noted between the TNFα level and maximal aerobic speed (r=-0.562; p=0.008).

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Introduction

Strenuous physical exercise causes muscular damage [5]. The gravity of these deteriorations varies from simple escape of certain sarcoplasmic enzymes like creatin kinas and dehydrogenates lactate up to real degenerative lesions of muscular fibers. The response to tissue injury after exercise is analogous to the immune response to inflammation resulting from infection [3]. A complex cascade of non-specific events were induced providing early recognition by restricting tissue damage to the site of injury. The local response involves the production of cytokines that are released at the site of inflammation [24]. In fact, muscle injury causes a sequential release of the pro-inflammatory cytokines such as Interleukin1β (IL-1β), Interleukin6 (IL-6) and Tumor Necroses Factor alpha (TNFα), followed very closely by anti-inflammatory cytokines such as Interleukin-10, and IL-1 receptor antagonist (IL-1ra). The inflammatory cytokines help regulate a rapid migration of neutrophils and then, later, monocytes into areas of injured muscle cells and other metabolically active tissues to initiate repair [4].

Several studies have been hypothesized that vigorous exercises were associated with a significant production of pro-inflammatory cytokines. Although the majority of available data was obtained following exhaustive aerobic exercise, or eccentric exercise [12,22,28]. However, little information is available regarding effect of exhaustive maximal exercise on these cytokines, and the influence of the basic kind of exercise and subject trained state.

The purpose of this study was to investigate the impact of two kinds of exhausting maximal exercise on pro-inflammatory cytokines concentrations in endurance-trained athletes, resistance-trained athletes, and untrained subjects.

Materials and Methods

Subjects: Data are collected on seven sedentary subjects (SS) (age 23.9±4.2 yr, body mass 79.1±19.1 kg, height: 176.6±11 cm), normally physically active but none engaged in regular athletic training, and fourteen sportsmen: seven endurance-trained athletes (EA) (age 22.7±3.7 yr, body mass 77.1±7.9 kg, height: 179.9±5.3 cm) and seven resistance-trained athletes (RA) (age 21±1.8yr, body mass 85.9±8.9 kg, height: 170.4±4.5 cm). All subjects were non-smokers, non-alcoholic drinkers and were showed no constraining anomalies at the medical

checking. Before any testing, the subjects received a verbal description of the experiment, and were required to complete a written consent for this study. The protocol was approved by the scientific comity of the Tunis Military Hospital.

Experimental protocol: Subjects were asked to report to the Sports Medicine Centre of the Ksar-Said Physical Education Institute on two separate occasions, in the morning and to refrain from exercise 48 h before the study. The first day of testing comprised the medical checking and an incremental exercise test called VAMEVAL test [11]. This later was a continuous running event with progressive intensity in which the participant exercised to the limit of his tolerance: Starting speed was 8.5km/h, and race's speed was 0.5km/1minute. It was adopted to determine the maximal aerobic speed (MAS) and to estimate the maximal oxygen uptake (VO_2 max).

One week after, subjects performed at identically conditions, the second exercise test called Time- Limited test [6]. This event was designed to produce an important lactacidemic concentration few seconds after the exercise beginning. It was also a continuous running event but with a constant intensity equal to 100% of the MAS performed on the first day of testing. The speed was regulated by means of a sound track that emits sounds at calculated intervals, and subject stops running at total exhaustion.

Four millilitres of blood were collected by venous puncture in tube without anticoagulant immediately before and after each test. Samples were centrifuged at 3000 rpm for 15 min at 4°C. To prevent erroneous results due to the presence of fibrin, centrifugation of samples took place after complete clot formation. Serum were withdrawn and stored at -80°C until analysis.

Analysis: Performed at the Tunis Military Hospital Laboratories of Haematology and Immunology. All stages of measurement were automatically carried out using an IMMULITE Analyzer.

Interleukin 1β: IL-1β serum level was determined by an IMMULITE IL-1β kit with Catalogue Number LKL11 (100 tests). IMMULITE IL-1β is a solid phase, two-site chemiluminescent enzyme immunometric assay designed for the quantitative measurement in vitro of IL-1β. Volume required of serum is about 75µl. Sample cup must contain at least 100µl more than the total volume required. Intra-assay (Within in-run) CV was 2.8% to 4.9%, interassay (Run-to-run) CV was 4.8% to 9.1%, and the analytical sensitivity was 1.5 pg/ml.

Interleukin 6: IL-6 serum level was determined in vitro by an IMMULITE IL-6 kit with Catalogue Number LK6P1 (100 tests). The principle of the procedure was a sequential immunometric assay with incubation cycles (2 x 30 min). Volume required of serum is about 100 µl. Sample cup must contain at least 250µl more

than the total volume required. Intra-assay CV was 3.6% to 6.2%, interassay CV was 5.9% to 9.6%, and the analytical sensitivity was 5 pg/ml.

Tumor Necroses Factor alpha: TNFα serum level was determined in vitro by an IMMULITE TNFα kit with Catalogue Number LKNF1 (100 tests). The principle of the procedure was an immunometric assay with one incubation cycle (1 x 60 minutes). Volume required of serum is about 100 µl. Sample cup must contain at least 250µl more than the total volume required. Intra-assay CV was 2.6% to 3.5%, interassay CV was 4.0% to 6.5%, and the analytical sensitivity was 1.7 pg/ml.

Statistical procedures: All values were expressed as means ±SD. Data of each group was analyzed using Wilcoxon matched-pairs tests. Differences between groups were compared using the Mann-Whitney test. Correlation analysis was used to estimate the correlation between some of the variables. Values at the 0.05 level were accepted as being statistically significant.

Results

Table 1
The maximal aerobic speed retched at the end of an incremental exhaustive exercise (VAMEVAL test), and the time performed during a constant intensity exercise test (Time-Limited test) by sedentary subjects (SS), endurance-trained athletes (EA) and resistance-trained athletes (RA)

Group	VAMEVAL test	Time-Limited test
	Maximal Aerobic Speed ($km \cdot h^{-1}$)	Time (s)
EA	19.6±1.2**	609.8±95.8**
RA	14.25±1.35*	552.4±82.5*
SS	12.11±1.8	357.85±82.5

Values are mean ±SD; *p<0.05, **p<0.01, ***p<0.001 compared with sedentary subjects

Physical performances: All subjects were performed the two exercise tests. The endurance-trained athletes were the most outstanding, sedentary subjects proved less performing, whereas resistance-trained athletes formed an intermediate class (Table 1). Data relating to the progressive event revealed maximal aerobic speeds significantly different between EA and the other two groups (p<0.01 for al.), and between RA and sedentary subjects (p<0.05).Whereas, data relating to the constant

intensity event were revelled significantly differences only between athletes and sedentary subjects (Mann-Whitney P less than 0.01 for EA, and than 0.05 for RA). No significant difference was found between EA and RA.

Table 2
Effect of an incremental exhaustive exercise test (VAMEVAL test) and a constant intensity exercise test (Time-Limited test) on serique interleukin1β concentration in sedentary subjects (SS), endurance-trained athletes (EA) and resistance-trained athletes (RA)

Interleukin 1β ($pg \cdot ml^{-1}$)	Group	VAMEVAL test		Time-Limited test	
		Before	After	Before	After
	EA	3.81±1.82	52.35±10.61*	4.8±2.34	74.74±13.93*
	RA	4.47±2.57	70.05±13.35*	7.02±4.23	80.44±16.02*
	SS	3.1±2.2	75.44±20.14*	6.4±4.99	86.94±12.46*

Values are mean ±SD; *p<0.05, **p<0.01, ***p<0.001 compared with values registered before exercising

Table 3
Interleukin 6 concentrations following an incremental exhaustive exercise test (VAMEVAL test) and a constant intensity exercise test (Time-Limited test) in sedentary subjects (SS), endurance-trained athletes (EA) and resistance-trained athletes (RA)

Interleukin 6 ($pg \cdot ml^{-1}$)	Group	VAMEVAL test		Time-Limited test	
		Before	After	Before	After
	EA	6.37±2.64	45.45±15.28*	8.38±3.2	56.02±21.48*
	RA	5.61±3.13	42.48±13.06*	6.9±2.18	62.94±17.94*
	SS	9.81±4.47	57.54±16.26*	8.22±2.8	84.5±15.18*

Values are mean ±SD; *p<0.05, **p<0.01, ***p<0.001 compared with values registered before exercising.

Pro-inflammatory cytokines: IL-1β level increased significantly in all groups under the effect of progressive or constant intensity exercise test (p=0.018 for al.)

(Table 2). The endurance-trained athletes had the downs concentrations (p=0.026 for SS, and p=0.017 for RA), and the EA values were more important after the Time-Limited test than the VAMEVAL test (p=0.017). A substantial correlation between the IL-1β level and MAS was observed after the incremental event (r=-0.497; p=0.022).

Significant increase in circulating IL-6 was also noted after the two events in all subjects (p=0.018 for al.) (Table 3). A substantial superiority, in favor of untrained subjects was observed in the end of the constant intensity exercise test (p=0.018 for EA, and p=0.037 for RA); and no differences were found between athletes. In addition, the constant intensity event data were more important than those determined after the incremental exercise in the SS (p=0.028) and the RA (p=0.018). A substantial correlation between the IL-6 concentration and MAS was observed after the Time-Limited test (r=-0.487; p=0.025).

Table 4
Tumor Necroses Factor alpha concentrations following VAMEVAL test and Time-Limited test in sedentary subjects (SS), endurance-trained athletes (EA) and resistance-trained athletes (RA)

	Group	VAMEVAL test		Time-Limited test	
		Before	After	Before	After
Tumor Necroses Factor alpha ($pg \cdot ml^{-1}$)	EA	4.4±2.13	51.1±11.21*	6.94±2.84	57.38±19.66*
	RA	5.75±2.64	65.41±6.88*	6.92±3.85	56.07±11.43*
	SS	7.08±3.22	70.68±11.72*	6.85±3.55	63.6±18.22*

Values are mean ±SD; *p<0.05, **p<0.01, ***p<0.001 compared with values registered before exercising

A significant changes in TNFα serum concentrations were also found after both maximal exercise tests in all groups (p=0.018 for al.) (Table 4). The type of exercise intensity wasn't affected the enhancement. Whereas, a significantly differences were noted in the end of the incremental exercise between endurance-trained athletes and the other two groups (p=0.018 for al.); and no differences were found between resistance-trained athletes and the untrained subjects. In the end of the incremental event, a significant correlation was noted between the TNFα level and MAS (r=-0.562; p=0.008).

Discussion

The results of the present study support the findings reported by a number of authors that the sport performance depends on the similarity between the exercise test and the exercise training [16]. The effort required during the incremental exercise test largely depends on the athlete's ability to ensure a lasting perfusion of muscles in activity. The improvement of each ability was acquired through well-structured endurance training over several years, and may explain the superiority of the EA maximal aerobic speed. However, the success in the second effort was be related to the athlete's abilities to transport and consume oxygen, and on his capacity to tolerate acidosis. The development of each quality was related to aero-anaerobic exercise training and gives the reason why athletes' performances were relatively similar.

Along with these organism's adaptations, several epidemiologic data suggest that vigorous physical exercise typically results in muscle soreness and injury. The response to tissue injury after exercise is analogous to the acute-phase response to inflammation resulting from infection [3]. The similarly events were mobilization and activation of leucocytes, induction of acute-phase response, increases in pro-inflammatory cytokine production, cellular infiltration, and tissue damage [7]. Despite these events, other symptoms, such as vasodilatation, organ dysfunction, and leukocyte aggregation, does not occur [26]. Therefore, exercise is considered to be a model of limited inflammatory response.

Our study replicated results of several studies showing a vigorous exercise-induced increase in serum IL-1β concentration. These data were obtained from a prolonged moderate exercise such as marathon run [23,25], or from exhaustive eccentric exercise [19], or from a wrestling practice which involves both aerobic and anaerobic exercise and concentric and eccentric types of movements [12]. In contrast, Suzuki *et al.* [29] were observed no significant changes in the plasma concentration of IL-1β immediately after a short-duration intensive exercise. Plasma IL-1β raised only 2 h after exercise, but plasma IL-1ra increased more rapidly and markedly than IL-1β. This suggests that IL-1β bioactivity should be blocked at least in the circulation. Furthermore, recent studies using more sensitive and specific assays have found only minor, if any, changes in IL-1β plasma concentration [21,24,31]. This may be due to many reasons reported to experimental protocols, or to the fact that IL-1β is rapidly cleared from the circulation and it finding's in the urine of runners support this idea [25]. Statistical analyses were also demonstrated that IL-1β level was dependent of subject trained state. This agrees with several other studies which suggested that the increase in

IL-1β level was related to systemic and not local events [19] and the fact that IL-1β produced by muscle cells is not pro-inflammatory but involved in muscle adaptation [2].

The present work suggests that exhaustive maximal exercise induces an increase of TNFα plasma concentration. Previous studies were demonstrated a significant increase in the levels of the cytokine after an aerobic exercise [12,20,23,25]; however, other works suggests that TNFα level remain unchangeable after an endurance exercise [13], or after an eccentric exercise [19], or after a short-duration intensive exercise [29]. Furthermore, our data demonstrate a clear dependence between TNFα production and the subject endurance-trained state. This probably may be related to the fact that TNFα may be sensitive to the metabolic mechanisms, a principally to the glycogen [22,28] and the lipid stores [9].

In according to several studies, an important increase in IL-6 level accompanied the IL-1β and TNFα race during vigorous exercise [12,25]. These cytokines were produced by many different types of cells, and the major sources are known to be stimulated monocytes/macrophages, fibroblasts, and vascular endothelial cells [1]. However, recently works using biopsies were suggested that myofibers themselves were expressed IL-6 during muscle damage [23,30]. IL-6 was the main mediator of the acute-phase [15]. Its elevation helps induce synthesis of acute-phase proteins (inflammatory); and upregulates some anti-inflammatory cytokines; however, the increased IL-6 concentrations were reported to be closely related to the degree of muscle injuries [5,8]. Given the fact that muscle damages depend on exercise type, and the subject trained state [5], the correlation between IL-6 and MAS was not surprising. In fact, the injured fibers repair processes are indicated by the muscle growing resistance to later exercises. The realization of a well-defined constant exercise results in injuries the fixing of which makes the muscle more resistant to later exercises of the same kind [18]. Indeed, to train a muscle according to a well-defined mode of exercises, protects it from injuries resulting from the practice of similar exercises [17], but makes it more sensitive to injuries resulting from different types of exercises [33].

In conclusion; maximal physical exercise is the origin of the significant increase when carried out up to exhaustion in IL-1β, IL-6 and TNFα in the blood. Such an increase is the evidence of cellular attacks, the gravity and development of which vary according to the type of effort made by the subject as well as the latter's training state.

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