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Opposite effect of acute aerobic exercise on plasma endothelin levels in trained and untrained men

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Background:

Summary

Endothelin, a natural peptide exhibiting potent vasoconstrictor activity, may play a crucial role in cardiovascular disease. The purpose of the present study was to compare the effect of an aerobic exercise bout on plasma ET levels in trained and untrained subjects.

Material/Methods:

Nine healthy physically active males and nine sedentary controls cycled at 60% of their maximal aerobic power for 30 min. Plasma endothelin was determined by enzyme immunoassay at rest and 30 min after the end of the exercise. Endothelin values were compared through two-way (training status × time) analysis of variance with repeated measures on time. Changes in plasma volume, calculated from hematocrit and hemoglobin data, were compared through independent Student's *t* test.

Results:

We found a significant interaction of training status and time ($p=0.05$) resulting from opposite changes in the trained and untrained group (decrease in the former from 4.3 ± 1.1 to 2.0 ± 0.6 pg/ml vs. increase in the latter from 2.6 ± 0.6 to 3.3 ± 1.1 pg/ml). Changes in plasma volume with exercise were significantly different (decrease in the trained group vs. increase in the untrained group, $p=0.03$).

Conclusions:

Our data indicate that aerobic training may reverse the augmentative effect of acute exercise on plasma endothelin levels. This adaptation may represent a novel beneficial effect of regular physical activity on human health.

key words:

endothelin • aerobic exercise • plasma volume • training status

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BACKGROUND

One of the vasoactive substances produced by the endothelium is endothelin (ET), a 21-amino-acid peptide present as three isoforms, ET-1, ET-2, and ET-3. ET-1 is the predominant isoform and is secreted by vascular endothelial and epithelial cells, interstitial fibroblasts, phagocytes, cardiomyocytes, and cancer cells. ET-1 exhibits potent vasoconstrictor activity, induces bronchospasm and mitosis, possesses growth-promoting properties in different cell types, and may play a crucial role in cardiovascular disease [1,2].

A great number of studies conducted on humans have investigated the effect of acute exercise on plasma ET concentration [3–10]. Most studies have found increased ET-1 values after exercise in both healthy individuals [3,7,8] and patients with cardiovascular disease [5,9]. One study reported no significant change [4], another reported a biphasic response consisting of an initial reduction and then an increase to pre-exercise levels [10], and another reported opposite effects depending on exercise mode (jogging vs. cycling) [6].

Recent studies have examined the effect of chronic exercise on plasma ET concentration [11–13]. Aerobic training decreased resting plasma ET-1 concentration in young men [11] and older women [12], as well as prevented the abnormal increase in plasma ET-1 induced by acute exercise in normotensive offspring of hypertensive parents [13]. The purpose of the present study was to examine whether aerobic exercise training modulates the response of plasma ET to acute exercise in healthy individuals with no family history of hypertension.

MATERIAL AND METHODS

Subjects

Nine young non-obese (body mass index, BMI <30 kg m⁻²), non-smoking, moderately trained males, who responded to a public invitation, participated in the study. They had been exercising at a moderate intensity for at least six months, three to four times per week, at least 45 min per session. An additional group of nine untrained male volunteers of similar age, body mass, and height to the trained group served as controls. All subjects were not suffering from any chronic or acute disease and were not receiving medication or nutritional supplements. In particular, all were normotensive and none had a family history of hypertension. They were informed of the design of the study orally and in writing and consented to participate. The study was designed and carried out according to the guidelines of the University of Thessaloniki Ethics Committee.

Experimental protocol

Subjects were initially familiarized with the cycle ergometer that was used in the study (Kettler KX1, Ense-Parsit, Germany) and then performed a graded test for the assessment of maximal aerobic power (W_{max}). Subjects started at a power output of 40 W for 5 min and power was increased by 40 W every 2 min thereafter. Resistance was controlled by a microprocessor so that power output, once set, was independent of pedaling frequency (within certain lim-

its). Heart rate was monitored by a Polar Accurex monitor (Kempele, Finland). When subjects reached 5 beats/min below their theoretical maximal heart rate (220 – age) or when it was subjectively obvious that pedaling was becoming so difficult that a normal increment in power output would cause termination of exercise, increments were limited to 15 W. The test was terminated when pedaling frequency fell below the minimum required to maintain the set power output for 10 s.

Three days after the maximum test, the subjects cycled at 60% of W_{max} for 30 min after a 5-min warm-up. Exercise was performed in the morning after an overnight fast and the subjects had free access to water. All subjects refrained from vigorous exercise (in particular, training sessions for the trained group) three days before the maximum test and between the two trials.

Blood sampling

Volunteers provided two blood samples in a sitting position from an antecubital vein into chilled evacuated test tubes containing EDTA. The first blood sample was obtained at rest and the second 30 min after the end of the 30-min exercise. An aliquot of each sample was removed for hemoglobin and hematocrit measurement, while the rest was centrifuged immediately at 4°C. Plasma was separated promptly and stored at –20°C until assayed for ET.

Assays

ET was measured in duplicate by enzyme immunoassay using a kit from Cayman (Ann Arbor, MI) after extraction and purification from plasma on Sep-Pak C₁₈ cartridges from Tech Elut (Cheshire, UK). The intra- and inter-assay coefficients of variation of the method were 4 and 5%, respectively. Changes in plasma volume were determined after measuring hemoglobin with a kit from Spinreact (Santa Coloma, Spain) and hematocrit by microcentrifugation. The following formula was used: Plasma volume post-exercise relative to plasma volume pre-exercise = [(100 – hematocrit post) × hemoglobin pre] / [(100 – hematocrit pre) × hemoglobin post], where hematocrit is expressed in percent [14].

Statistical analysis

All values are expressed as the mean ± SEM. Anthropometric and performance data as well as changes in plasma volume were compared through independent Student's *t* test. Heart rate during exercise and ET values were compared through two-way (training status × time) analysis of variance with repeated measures on time. A significant interaction was followed-up with pair-wise comparisons through simple main-effect analysis. Linear correlation analysis was done by Pearson's product-moment correlation. Differences were considered significant at *p* ≤ 0.05.

RESULTS

Anthropometric and performance data of the participants are presented in the Table 1. There were no significant differences between the trained and untrained groups in age, body mass, height, or BMI, as a result of the experimental design. Both W_{max} and power at the 30-min exercise bout

Table 1. Anthropometric and performance data of participants (mean ±SEM).

	Trained group (n=9)	Untrained group (n=9)
Age (year)	29.0±2.1	25.2±1.7
Body mass (kg)	79.5±3.2	74.3±1.6
Height (m)	1.79±0.1	1.79±0.1
BMI (kg m ⁻²)	24.9±1.0	23.4±0.9
Maximal power (W)	276±14*	206±10
Power at the 30-min trial (W)	163±7*	128±6

* $p < 0.001$, significantly different from the untrained group.

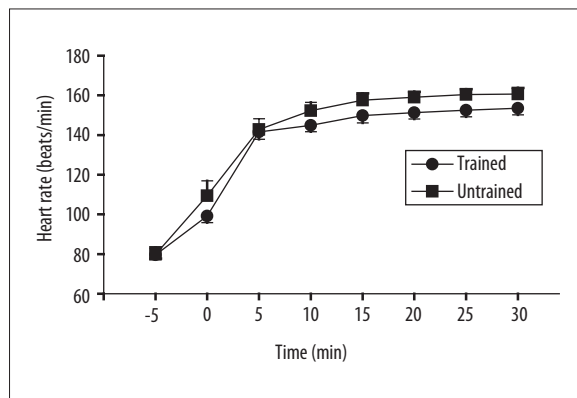


Figure 1. Mean heart rate of trained and untrained subjects at rest (-5 min), after 5 min of warm-up, and during 30 min of cycling at 60% of Wmax. Error bars denote SEM.

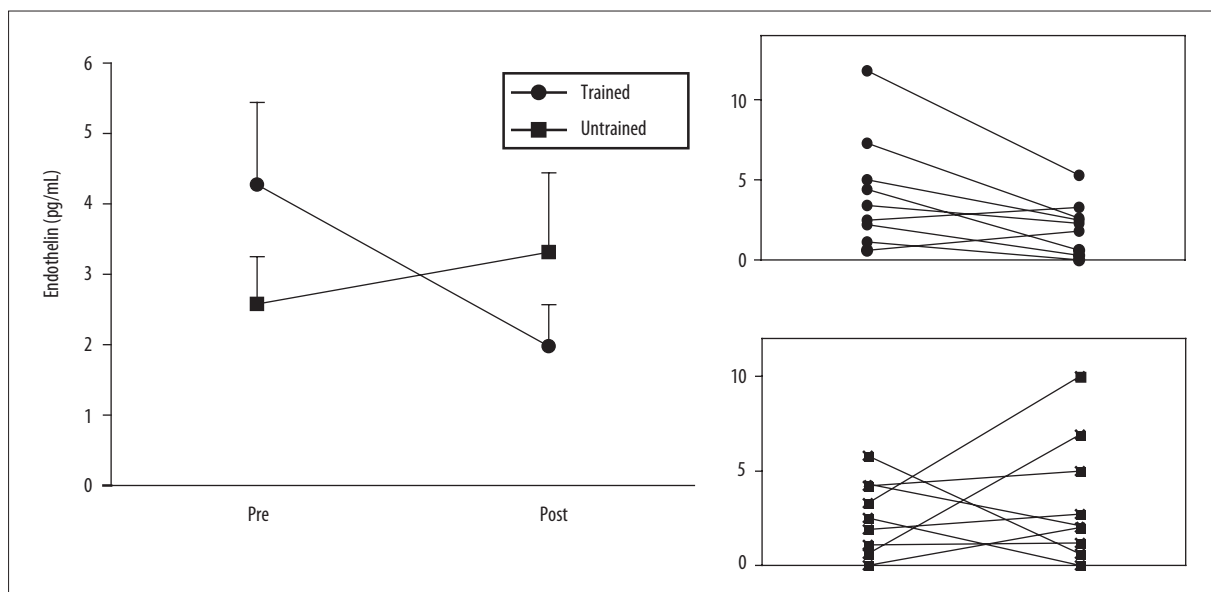


Figure 2. Left panel: Mean pre- and post-exercise plasma ET concentrations of trained and untrained subjects. Error bars denote SEM. Right panels: Individual values of the two groups.

were significantly higher in the trained than in the untrained group ($p < 0.001$). The two groups had the same mean resting heart rate (80 beats/min). The trained group exhibited consistently lower heart rates during the exercise trial (Figure 1), although not significantly different from the untrained group ($p = 0.16$). Average heart rate during the exercise trial was 149 and 155 beats/min, respectively.

With regard to ET, we found a significant interaction of training status and time ($p = 0.05$), resulting from opposite changes in the trained and untrained group. That is, ET decreased in the trained group 30 min after the 30-min exercise bout (from 4.3 ± 1.1 to 2.0 ± 0.6 pg/ml), whereas it increased in the untrained group (from 2.6 ± 0.6 to 3.3 ± 1.1 pg/ml), as illustrated in Figure 2. These changes were exhibited by the majority of the subjects in each group (i.e. seven trained subjects showed a decrease and six untrained subjects showed an increase). None of the pair-wise comparisons with regard to training status or time produced significant differences. Changes in ET concentration correlated significantly with

pre-exercise concentrations in the trained group ($r = -0.87$, $p = 0.002$), but not in the untrained group.

The trained group experienced a slight reduction in plasma volume with exercise (0.99 relative to rest), while the untrained group experienced a plasma expansion (1.05 relative to rest). The difference between the two groups regarding plasma volume changes was significant ($p = 0.03$).

DISCUSSION

In the present study we compared for the first time the effect of acute aerobic exercise on plasma ET levels in subjects of different training status who were healthy and with no family history of hypertension. Attesting to the difference in training status between the two groups is the significant difference in Wmax and the fact that the trained group cycled at a lower heart rate than the untrained group, while producing a power output higher by 27%. We chose male volunteers in order to avoid the confounding effect of es-

trogens on vascular function and plasma ET levels [15–17]. Moreover, we chose our subjects to be neither smokers nor obese nor suffering from cardiovascular disease because plasma ET levels are elevated in these population categories [18]. Finally, we chose to take the post-exercise blood sample 30 min after the completion of exercise, as ET has been found to reach its peak in plasma at that time [8].

We observed opposite effects of acute exercise on plasma ET levels in the trained and untrained groups (decrease vs. increase, respectively). This is in agreement with the finding that 30 min of cycling at 145 beats/min decreased plasma ET-1 concentration in mostly trained subjects [6]. It also fits with the recent report that training prevented the abnormal increase in plasma ET-1 induced by acute exercise in normotensive offspring of hypertensive parents [13]. Additionally, our finding of a decreasing effect of an exercise bout on plasma ET in trained but not untrained subjects may provide a mechanism for the reported lower resting concentrations in trained humans [11,12]. It should be pointed out that, although the trained group had a higher resting ET concentration than the untrained group in the present study, this difference was not significant and may be attributed to inter-individual differences. Finally (concerning our ET data), worthy of attention is the strong negative correlation between the resting ET concentration and its change with exercise in the trained group, which suggests a greater decreasing effect of exercise on higher ET levels.

The training-dependent response of plasma ET to acute exercise observed in the present study was accompanied by training-dependent alterations in plasma volume. Changes in ET concentration with exercise are reportedly influenced by the hydration status: the greater the dehydration, the greater the increase in plasma ET concentration [8]. In this sense, it may appear surprising that ET decreased in the trained group despite a slight decrease in plasma volume, whereas it increased in the untrained group despite an increase in plasma volume. However, one has to bear in mind that changes in plasma volume were assessed 30 min after cessation of exercise and that changes during recovery are inversely related to changes during exercise [19]. It is therefore possible that the ET increase in the untrained group was triggered by hemoconcentration during exercise (followed by hemodilution during recovery), whereas ET was “allowed” to decrease in the trained group since no hemoconcentration occurred during exercise.

Fluctuations in plasma ET levels have been proposed to contribute to the redistribution of blood flow during exercise, but the mechanism regulating ET release during exercise is not known [7]. It has been hypothesized that both neurohumoral factors (such as catecholamines and angiotensin II) and mechanical factors (such as hemodynamic shear stress) may trigger ET release [20]. Nevertheless, the precise role of ET in the physiological responses (both acute and chronic) to exercise as well as its origin during exercise remain to be elucidated.

CONCLUSIONS

Our data provide evidence for a reducing effect of aerobic exercise training on post-exercise plasma ET levels, as opposed to the increase observed in untrained individuals in both the present and other studies. This adaptation may represent a novel beneficial effect of regular physical activity on human health, which may explain vascular effects of physical conditioning and may be of particular interest in pathological situations exhibiting abnormally high ET levels.

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