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ORIGINAL ARTICLE

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Monoamine responses to acute and chronic aerobic exercise in normotensive and hypertensive subjects

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Objectives: The purpose of the present study was to compare the plasma and serum monoamine levels in sedentary, untrained normotensive and hypertensive men at rest with levels measured after an acute bout of exercise and to compare similar measurements following a 12-week aerobic training program. **Place of study**: The data obtained for this study was collected from a clinic for the prevention of heart disease and cardiac rehabilitation (FITCOR) and analyzed in the Federal University of São Paulo (EPM), Laboratory of Experimental Neurology. **Subjects**: Two groups of untrained male subjects, i.e., normotensive (N=16) and hypertensive (N=19), were submitted to an acute bout of exercise to analyze the acute effect of exercise on the monoamine levels. To study the chronic effect of exercise (physical training program), some individuals of each group were arranged in two other groups; normotensive (N=11) and hypertensive (N=8). **Measurement**: Plasma catecholamines and serum serotonin levels were determined by high performance liquid chromatography coupled with electrochemical detection. **Results**: A significant reduction in diastolic blood pressure at rest was observed in the hypertensive group after the physical training program ($p < 0.05$). Only the mean plasma noradrenaline concentration increased significantly post-exercise in all groups of individuals (acute effect of exercise - $p < 0.01$ for untrained normotensive and hypertensive; chronic effect of exercise - $p < 0.001$ for untrained and trained normotensive, $p < 0.01$ for untrained and trained hypertensive). **Conclusion**: These data show the beneficial effect of physical exercise in reducing the blood pressure in hypertensive patients, which does not seem to be related to changes in circulating monoamines.

UNITERMS: Monoamines. Aerobic exercise. Physical training. Hypertension. Humans.

INTRODUCTION

Several studies have shown that acute and chronic physical exercise may affect catecholaminergic and serotoninergic systems [1, 2, 3, 4]. The involvement of monoamines in hypertension has been repeatedly reported [5].

Sympathetic nervous system overactivity is reported to be an important mechanism in the initiation of blood pressure elevation in essential hypertension [6, 7]. The relationship between blood pressure and concentration of circulating monoamines has not been conclusively established although there are reports that link hypertension to catecholamine levels [6, 8].

Lower blood pressure following training is frequently associated with lower heart rate and cardiac output at rest and during submaximal exercise [9]. Although the mechanisms by which repeated exercise may lower blood pressure have not been clearly defined, these physiological adaptations are similar to those achieved through β-adrenoceptor blocking. These similarities suggest that exercise lowers blood pressure through a reduction of sympathetic neural activity [9].

Like catecholamines, serotonin is also present in the peripheral system and plays its physiological role on vascular smooth muscle [10, 11]. It is also known that both

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central and peripheral serotoninergic systems are involved in cardiovascular regulation and the action of other vasoactive substances like noradrenaline and angiotensine II are amplified by serotonin. Therefore, abnormal serotoninergic activity may participate in the pathogenesis of essential hypertension [11].

Physical training modulates the activity of these neurotransmitters at rest and during exercise, demonstrating an exponential relationship with increasing workload [12, 13, 14].

Since peripheral monoamines are involved in mechanisms that control blood pressure, and physical exercise affects monoaminergic systems, this work aimed at studying the involvement of monoamine levels in the beneficial effect of an aerobic training program. To achieve such goals we determined the level of circulating monoamines at rest, post-exercise and after a period of aerobic physical training in sedentary normotensive and hypertensive subjects.

Part of the data for the chronic effect of exercise was refereed in the Brazilian Journal of Medical and Biological Research (1996) in a Short Communication form.

MATERIAL AND METHODS

Two groups of untrained male subjects, i.e. normotensive (UT/N, N=16) and hypertensive (UT/H, N=19), were submitted to an acute bout of exercise to analyze the acute effect of exercise on the monoamine levels. Some individuals of each group were arranged in two other groups (respectively T/N, N=11 and T/H, N=8) to study the chronic effects of exercise (physical training program). Since some individuals did not follow the protocol determined for the study, these were not included in studying the chronic effect of exercise. All individuals were recruited from a clinic for the prevention of heart disease and cardiac rehabilitation (FITCOR) and were informed about the study design and objective and freely decided to participate in this study. None was involved in a regular aerobic exercise program before the study or was taking medications during the physical training program. According to the World Health Organization (WHO) criteria [15], all subjects classified as hypertensive would have a diastolic blood pressure = 95 mmHg recorded after 10 minutes in the sitting position on at least three different occasions. All measurements were made with a mercury sphygmomanometer and the diastolic blood pressure was recorded at the fifth phase of Korotkoff's sounds. Anthropometric data [16] were obtained in the two groups (N and H) before and after the period of the physical training program.

All subjects were submitted to an ergometric test before and after the physical training program. Each subject performed a maximal treadmill test (Inbramed Mod. KT-2000) using the Ellestad protocol [17]. Oxygen uptake was measured continuously during the test through the open-circuit method until exhaustion (Oxygen sensor N-22m, Oxygen analyzer S-3A/1, Carbon Dioxide sensor P-61B, Carbon Dioxide analyzer CD-3A (Ametek), DTM-325-MAOP-10 psi, American Meter). Heart rate, electrocardiogram (Hewlett - Packard System 4700 A Cardiograph) and blood pressure were measured during supine rest, during each minute of the treadmill test, and at the first, second, fourth and sixth minutes of recovery. Blood pressure recorded at rest and at the intensity of 60% of maximal oxygen uptake (VO_2max) was considered for statistical analysis.

Sampling Procedure

The subjects were instructed not to change any dietary or sleeping habits, except for a 12 hour fast before blood sampling. Blood samples (10 ml for catecholamines and 5 ml for serotonin assay) were drawn by venipuncture from each subject in the sitting position into heparinized tubes (catecholamines) and into dry tubes (serotonin) after 20 minutes of rest pre-exercise and immediately post-exercise in the sitting position, between 7:00 and 9:00 a.m., before and after the physical training program. The dry tubes were then placed on ice for 3 hours for clot retraction and the plasma and serum was obtained by refrigerated centrifugation at 3000 g for 15 min. Plasma and serum were then stored in liquid nitrogen until assay time, for no more than two months.

Physical training program

Subjects participated in a physical training program for a period of three months (36 sessions, 3 days per week) at an intensity of 60% of maximal oxygen uptake (VO_2max). Exercise bouts consisted of 40 minutes of aerobic exercise (20 minutes on a cycle ergometer and 20 minutes of walking and/or jogging) and 30 minutes of neuromuscular endurance exercise, flexibility and co-ordination. Heart rate was measured while the subject was on the cycle ergometer, walking and/or jogging at the beginning, during and at the end of all sessions of exercise in order to control the intensity of effort (60% VO_2max) as recommended by the American College of Sports Medicine [18]. The work load was adjusted during the

physical training program using the heart rate to maintain appropriate exercise intensity. The blood sampling was done at the same intensity of physical effort (assessed through heart rate) before and after the physical training program.

Sample Preparation

The sample was prepared as previously reported [19] for catecholamines and serotonin [20]. Circulating plasma catecholamines and serum serotonin levels were determined by High Performance Liquid Chromatography coupled with electrochemical detection (HPLC - ED).

Statistical Analysis

Statistical analysis was done by employing the ANOVA test with Tukey post test. Significance was established at the $p < 0.05$ level.

RESULTS

Anthropometric data are presented in table 1. There were no statistically significant differences in mean age, weight or height before and after the physical training program either in H or N groups. The sum of 7 skinfold thickness was compared between the H and N groups and differed significantly only with the acute effect of exercise. However, there were no significant differences in the body mass index of the same group, or between the N and H groups before and after the physical training program.

Blood pressure - UT/N and UT/H showed significant differences in diastolic blood pressure (DBP) at rest and during physical effort (figure 1). When the two groups (T/N and T/H) were compared for the chronic effect of exercise, they showed significant differences at rest before the physical training program in DBP. After the physical training program, there were no significant differences in DBP and sistolic blood pressure (SBP) between T/N and T/H. DBP was significantly reduced at rest in the T/H group (figure 2).

Monoamines - Plasma noradrenaline (NA) concentration was significantly higher post-exercise in all four groups (tables 2 and 3). Plasma adrenaline (A) and serum serotonin (5-HT) concentrations were not significantly changed at rest and post-exercise in any of the four groups (tables 2 and 3). Monoamine concentrations in trained groups (T/N and T/H) obtained either at rest or after exercise were not significantly different from their respective untrained groups (UT/N and UT/H).

DISCUSSION

The results presented in this study showed a reduction of diastolic blood pressure in hypertensive

Table 1

Anthropometric data for the acute and chronic effect of exercise in normotensive and hypertensive subjects

	Acute Effect of Exercise		Chronic Effect of Exercise			
			Before Training	After Training	Before Training	After Training
	Normotensive	Hypertensive	Normotensive		Hypertensive	
N° of subjects	16	19	11	11	8	8
Age (years)	45.9 ± 5.2	47.0 ± 5.2	45.5 ± 5.6	45.5 ± 5.6	47.5 ± 3.9	47.5 ± 3.9
Weight (kg)	82.3 ± 10.8	89.6 ± 15.1	82.0 ± 11.7	81.7 ± 10.9	77.7 ± 12.8	74.7 ± 15.6
Height (cm)	173.5 ± 6.8	172.2 ± 6.1	172.9 ± 7.1	172.9 ± 7.1	167.5 ± 8.2	167.5 ± 8.2
S7SF (mm)	155.8 ± 30.1	185.5 ± 48.8*	151.0 ± 20.6	143.8 ± 18.8	178.7 ± 65.5	144.0 ± 47.4
BMI (kg/m^2)	27.3 ± 2.4	30.5 ± 4.5	27.4 ± 2.8	27.3 ± 2.5	27.7 ± 3.3	26.6 ± 4.8
VO_2max (ml.kg.min)	39.1 ± 12.4	37.4 ± 6.2	38.8 ± 11.5	44.0 ± 9.7	40.2 ± 4.0	51.0 ± 7.3

The means ± SD values of age, weight, height, sum of 7 Skinfolds (S7SF) (biceps, triceps, subscapular, suprailiac, midaxillary, abdominal, calf), Body Mass Index (BMI) and maximal Oxigen Uptake (VO_2 max). * Statistically significant difference between normotensive and hypertensive groups (ANOVA test) with $p < 0,05$.

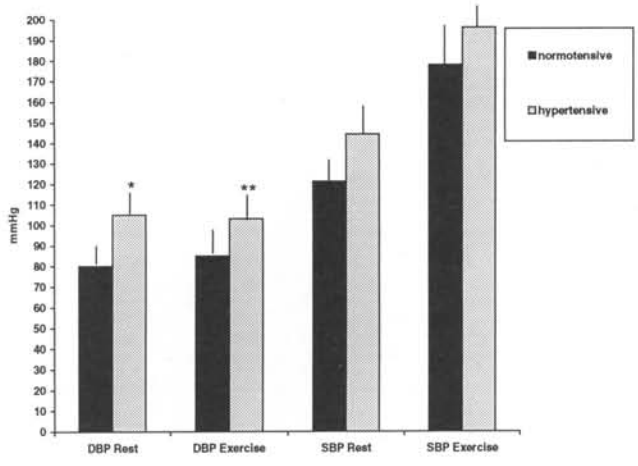

Figure 1 - Blood pressure values in normotensive and hypertensive subjects at rest and during effort analyzed for the acute effect of exercise at an intensity of 60% of maximal O_2 uptake (VO_2max). Data are expressed as mean ± SD.

* Statistically significant difference between normotensive and hypertensive groups (ANOVA test) with $p < 0.001$ for DBP at rest;

** Statistically significant difference between normotensive and hypertensive groups (ANOVA test) with $p < 0.05$ for DBP during exercise. DBP - Diastolic blood pressure. SBP - Systolic blood pressure.

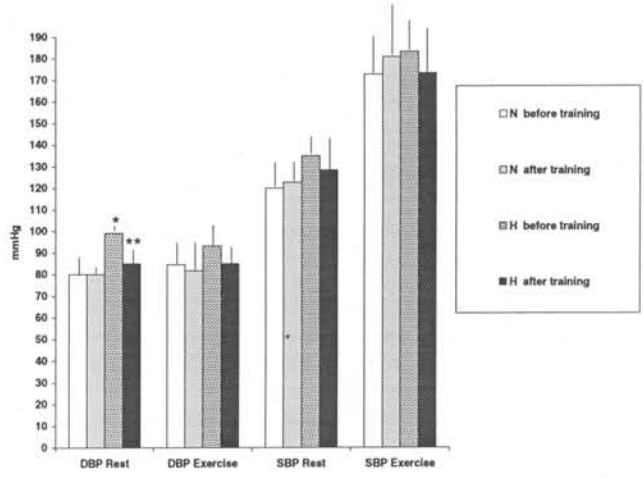

Figure 2 - Blood pressure values in normotensive and hypertensive subjects at rest and during effort, before and after physical training program. Data are expressed as mean ± SD.

·* Statistically significant difference of DBP at rest from normotensive group before physical training program (ANOVA test) for $p < 0.001$;

·** Statistically significant difference of DBP at rest after physical training program in hypertensive group (ANOVA test) for $p < 0.05$.

DBP - Diastolic blood pressure. SBP - Systolic blood pressure.

subjects at rest, after the physical training program. Such findings are in agreement with several other studies that have established regular exercise as the most effective non-pharmacological method for lowering blood pressure in both sedentary normotensive and hypertensive subjects. Despite the effectiveness of exercise therapy in mildly hypertensive subjects [21, 22, 23, 4], other factors have to be considered with respect to the differences in results from studies about hypertension, including: the type of essential hypertension, individual response to exercise and the quality and quantity of this exercise.

Conflicting data about plasma catecholamine concentration at rest and after exercise have been reported by various authors. Studies in which plasma catecholamines have been used as an index of sympathetic nervous activity have shown a reduction in sympathetic drive for the same absolute workload following training [12, 24, 25]. For a relative workload, however, the sympathetic nervous response was reported to be unchanged [25], decreased [12] or even increased after training [26].

In the present study, plasma noradrenaline at rest and for the same relative work load was not affected by the physical training program in the hypertensive group, although there was a tendency for higher levels after training. These results, therefore, suggest that after a physical training program the sympathetic nervous activity does not change at rest and for the same relative work load in hypertensive subjects but, as reported in other studies [27, 28], can be reduced for the same absolute work load.

The results presented in this work, showing no significant differences in plasma adrenaline levels post-exercise, are in agreement with studies of Kjaer et al. [29] and Urhausen et al. [30], who measured catecholamine concentrations during exercise of different intensities, relating catecholamine increasing at higher effort intensities (anaerobic threshold).

In agreement with our results, some investigations have demonstrated that the sympathetic nervous system activity is not increased in essential hypertension [31]. By reviewing 64 studies, Goldstein [6] observed that 80% of the studies reported higher plasma noradrenaline levels in hypertensive than in normotensive subjects, but statistically significant differences were found in only about 40% of them. Considering plasma adrenaline levels, the majority of studies have shown higher adrenaline levels in hypertensive patients as compared with normotensive subjects, and also only about 40% of studies have reported statistically significant differences.

Table 2

Plasma levels of Noradrenaline (NA) and Adrenaline (AD) and serum Serotonin (5-HT) for the acute effect of exercise (60% VO_2max) in normotensive and hypertensive subjects

	Normotensive		Hypertensive	
	Rest	Post-Exercise	Rest	Post-Exercise
NA	126.52 ± 38.63 (N= 16)	196.49 ± 71.11* (N= 16)	149.15 ± 48.54 (N= 19)	211.31 ± 57.68* (N= 19)
AD	45.65 ± 15.84 (N= 13)	46.23 ± 13.18 (N= 14)	46.64 ± 28.38 (N= 17)	44.63 ± 20.73 (N= 17)
5-HT	165.09 ± 56.16 (N= 15)	168.13 ± 89.15 (N= 15)	127.59 ± 38.29 (N= 19)	142.89 ± 45.51 (N= 19)

Data are expressed as mean ± SD in $pg.ml^{-1}$ for catecholamines and $ng.ml^{-1}$ for serotonin.

* Statistically significant difference from rest to effort in normotensive and hypertensive groups (ANOVA test) with $p < 0.01$. N = number of subjects.

Table 3

Plasma levels of Noradrenaline (NA) and Adrenaline (AD) and serum Serotonin (5-HT) for the chronic effect of exercise in normotensive and hypertensive subjects

	Before Training		After Training	
	Normotensive	Hypertensive	Normotensive	Hypertensive
NA Rest	120.52 ±31.27 (N= 11)	129.52 ±24.32 (N= 8)	138.39 ±31.47 (N= 11)	167.19 ±47.60 (N= 8)
NA Post-Exercise	217.38 ±75.84* (N= 11)	234.28 ±50.96** (N= 8)	230.86 ±61.86* (N= 11)	263.77 ±53.87** (N= 8)
AD Rest	46.59 ±17.44 (N= 10)	41.46 ±12.76 (N= 8)	41.51 ±14.10 (N= 9)	39.96 ±27.62 (N= 8)
AD Post-Exercise	46.88 ±14.58 (N= 10)	43.36 ±17.32 (N=8)	50.03 ±46.09 (N= 9)	35.91 ±13.02 (N= 8)
5-HT Rest	152.03 ±72.87 (N= 11)	122.35 ±15.15 (N= 8)	127.48 ±55.96 (N= 11)	106.08 ±40.79 (N= 8)
5-HT Post-Exercise	152.39 ±96.48 (N= 11)	126.86 ±61.04 (N= 8)	126.95 ±78.91 (N= 11)	114.00 ±53.41 (N= 8)

Data are expressed as mean ± SD in $pg.ml^{-1}$ for catecholamines and $ng.ml^{-1}$ for serotonin.

* Statistically significant difference from rest to post-exercise before and after training in normotensive group (ANOVA test) with $p < 0.001$;

** Statistically significant difference from rest to post-exercise before and after training in hypertensive group (ANOVA test) with $p < 0.01$. N = number of subjects.

In contrast to other studies, the possibility that serotonin could mediate the influence of physical exercise on cardiovascular function is not favoured by the present findings. No significant differences in serum serotonin levels between resting and post-exercise measurements, either before or after the physical training program, were found in hypertensive or normotensive subjects, or upon comparison of the two groups.

Strong evidence seems to implicate serotonin in hypertension, and perhaps the most relevant fact is the

efficacy of serotonin antagonists in lowering blood pressure in hypertensive patients both acutely and chronically [32]. In contrast, the correlation between physical exercise and serotonin has not been conclusively established. The serotonin response to exercise has been investigated minimally. Considering our results, probably the aerobic exercise (60% VO_2max) does not provoke significant alterations in peripheral serotonin levels. A reduction in its level would probably be necessary to suppress the vasoconstrictor effects of serotonin, and therefore, lower the blood pressure.

The results of this study suggest that aerobic exercise programs have an important effect in the reduction of blood pressure. However, this influence cannot be directly related to changes in plasma monoamines.

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RESUMO

Objetivos: O propósito do presente estudo foi comparar os níveis sanguíneos de monoaminas de homens sedentários normotensos e hipertensos na situação de repouso, com indivíduos submetidos a uma sessão de exercício físico e após um programa de 12 semanas de treinamento aeróbio. **Local**: Os dados obtidos para este estudo foram coletados de uma clinica para prevenção e reabilitação de doença cardiovascular (FITCOR) e analisados no Laboratório de Neurologia Experimental da Escola Paulista de Medicina (UNIFESP). **Participantes**: Dois grupos de homens sedentários, normotensos (N=16) e hipertensos (N=19), foram submetidos a uma sessão de exercício físico para analisar o efeito agudo do exercício sobre os níveis de monoaminas circulantes. Alguns indivíduos de cada grupo (normotensos (N=11) e hipertensos (N=8)) foram incluídos para o estudo do efeito crônico do exercício. **Mensuração**: Os níveis sanguíneos de monoaminas foram determinados por cromatografia líquida de alta eficiência com detecção eletroquímica. **Resultados**: Foi observado uma significativa redução da pressão arterial diastólica em repouso no grupo hipertenso após o programa de treinamento físico. Somente a concentração plasmática de noradrenalina apresentou um aumentou significativo após uma sessão de exercício físico em todos os grupos. **Conclusão**: Estes dados mostram o efeito benéfico do exercício físico em reduzir a pressão sanguínea em pacientes hipertensos, o qual não parece estar relacionado com as alterações de monoaminas circulantes.

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