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EFFECT OF PHYSICAL ACTIVITY ON PLASMA ADRENOMEDULLIN CONCENTRATION AND ITS RELATIONSHIP WITH NITRIC OXIDE IN ATHLETES

SPORCULARDA PLAZMA ADRENOMEDULLİN KONSANTRASYONU ÜZERİNE FİZİKSEL AKTİVİTENİN ETKİSİ VE NİTRİK OKSİT İLE İLİŞKİSİ

ORIGINAL INVESTIGATION
ÖZGÜN ARAŞTIRMA

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ABSTRACT
ÖZET

Objective: The aim of this study was to determine whether regular physical activity or acute exercise influenced plasma adrenomedullin (AM) concentration and whether it was related to gender, blood pressure and nitric oxide (NO) production.

Material and Methods: Sixty healthy students participated in this study. They were divided into two groups. The first group consisted of 30 students, 16 female, 14 male athletes carrying out regular exercise. The second group was made up of 15 females, 15 males nonathletes. All students submitted to a cycle exercise test until volitional exhaustion. Heart rate (HR), blood pressure, maximal oxygen uptake (VO_2max) and carbon dioxide production (VCO_2) were measured continously. Before starting, at the 1st min and at the 30th min of exercise, venous blood samples were taken to determine AM and NO production.

Results: AM in the female and male athletes were significantly higher than in the female and male non-athletes. The plasma AM concentration in female athletes was found be significantly higher than in male athletes. Acute exercise did not affect AM concentration in subjects. We did not find any relationship between AM/BMI (Body mass index) and other variables such as systolic, diastolic pressure, heart rate, VO_2max and VCO_2 but there was a negative relationship with NO production.

Conclusion: The present data suggest that an increase in AM during prolonged physical activity may be a compensatory mechanism against further elevation of blood pressure.

Key words: Adrenomedullin, Blood Pressure, Exercise, Oxygen Consumption

Amaç: Bu çalışmanın amacı düzenli fiziksel aktivite ya da akut egzersizin plazma adrenomedullin (AM) konsantrasyonunu etkileyip etkilemediğini ve AM'in cinsiyet kan basıncı ve nitrik oksit (NO) yapımı ile ilişkisini araştırmaktır.

Gereç ve Yöntem: Bu çalışmaya 60 sağlıklı öğrenci katıldı. Bunlar iki guruba ayrıldı. Düzenli spor yapan 16 kız 14 erkek toplam 30 öğrenci birinci gurubu oluşturdu. Sporcu olmayan 15 kız 15 erkekte ikinci gurubu oluşturdu. Öğrenciler bitkinlik oluşuncaya kadar bisiklet egzersiz testine tabi tutuldu. Kalp hızı, kan basıncı, maksimal O_2 tüketimi (VO_2max) ve CO_2 üretimi (VCO_2) egzersiz boyunca ölçüldü. Akut egzersize başlamadan önce, birinci ve 30. dakikasında öğrencilerden AM ve NO seviyelerinin tesbiti için venöz kan örnekleri alındı.

Bulgular: Kız ve erkek sporcuların AM seviyesi, sporcu olmayanlarınkinden önemli derecede yüksekti. Kız sporcuların plazma AM konsantrasyonları erkek sporcularınkinden önemli derecede farklı bulundu. Kişilerdeki AM konsantrasyonunu akut egzersiz etkilemedi AM\BMI (vücut kitle indeksi) ile sistolik-diyastolik basıçlar, kalp hızı VO_2max ve VCO_2 arasında önemli bir ilişki bulunmadı.

Sonuç: Bu çalışmadaki veriler, düzenli fiziksel aktivite esnasında artmış AM'nin, kişilerin kan basıncındaki yükselmeyi düzenleyen kompensatuvar bir mekanizma olabileceğini göstermektedir.

Anahtar kelimeler: Adrenomedullin, Egzersiz, Kan Basıncı, Oksijen tüketimi

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Introduction

Human adrenomedullin (hAM) is a 52 amino acid peptide with a structural homology to calcitonin gene-related peptide (CGRP) (1). AM is produced in several tissues (kidney, lung, and heart) (2), and its production is upregulated by several factors such as oxidative stress, pro-inflammatory cytokines, angiotensin II, hypoxia, hyperglycemia, natriuretic peptide, and aldosterone, among other factors (3).

Increasing experimental and clinical evidence supports the important role of AM in the pathophysiology of a variety of cardiovascular diseases. In spite of its relatively low plasma levels (1), various clinical studies have shown that they correlate with severity in diseases such as heart failure (HF), acute myocardial infarction and hypertension (4-8).

At the cardiovascular level, AM can be synthesized and secreted from various cells, including vascular endothelial cells, vascular smooth muscle cells, cardiomyocytes and fibroblasts (3, 9). Furthermore, AM and its receptors are expressed in the normal and failing myocardium (10, 11). Orshal et al. (12) have shown that blood vessel contractility is gender dimorphic and/or influenced by sex hormones, and both testosterone and oestradiol have a number of effects on the vasculature. The relationship between AM and gender has not been fully investigated. These gender differences during regular physical activity may help explain the disparity in the prevalence of disorders between women and men.

Several humoral factors (catecholamines, corticosteroids, angiotensin II, endothelin-I) as well as volume expansion (acute pressure overload) and shear stress can stimulate AM production and secretion, but the physiological mechanism stimulating AM secretion has not yet been completely elucidated (13-15). Among the physiological tests applied to provoke a prompt activation of the sympathetic nervous system and secretion of many vasoactive hormones, exercise is considered to be one of the best. Until now, only a few studies have been conducted on the effect of prolonged or acute exercise on the plasma AM concentration.

Tanaka et al. (16) reported an increase in plasma AM concentration during three steps of submaximal cycle exercise (lasting 12 min) in healthy subjects. Recently, Piquard et al. (17) described a significant increase in plasma AM during maximal exercise performed with leg muscles both in heart transplant recipients and normal subjects. The above data differ from those obtained by Nishikimi et al. (18) and Morimoto et al. (19) who failed to find any changes in plasma AM concentration during two steps of submaximal dynamic exercise (lasting 8 min) in hypertensive and normotensive subjects. Poveda et al. (20) also failed to show any increase in AM after a stress test on a treadmill. Krzeminski et al. (21) suggested that AM may not respond to stimuli such as short-term exercise because secretion of AM is regulated by gene expression. Moreover, these authors concluded that AM may not be involved in the regulation of the cardiovascular system during exercise. Krzeminski et al. (22, 23) demonstrated that the static handgrip exercise induced an increase in plasma AM, but that dynamic incremental exercise performed to exhaustion induced a small decrease in the plasma AM in healthy subjects.

The purpose of the present study was to investigate the effect of regular physical activity and acute exercise on plasma AM concentration and to determine whether the exercise-induced changes in plasma AM were related to blood pressure, gender difference and nitric oxide production in athletes and non-athletes.

Materials and Methods

Subjects

A group of 30 healthy students (15 female, 15 male) and another group of 30 athlete students (16 female, 14 male) who regularly carried out physical activity volunteered to participate in this study. All volunteers for the study read and signed the informed consent forms. The research procedure was approved by the Ethics Committee at the Medical Resarch Centre, Erciyes University. All procedures were carried out under similar environmental conditions (23-24ºC and 50-60% humidity) between 13:00-15:00 pm.

The students visited the laboratory twice before the tests. Each subject underwent a detailed medical history and physical examination. No student had a history of pituitary, renal, hepatic or metabolic disease. Subjects were nonsmokers and were not heavy alcohol users. They refrained from exercise for 24 h before each evaluation.

Experimental Protocols

The students submitted to the incremental graded exercise test performed on a bicyle ergometer until volitional exhaustion in order to determine their maximal oxygen uptake (VO_2max). The pedalling rate was increased by 10 km/h every 2 min starting with 30 km/h (at 100 watt) until volitional exhaustion. A three-lead electrocardiogram recorded data. A doctor supervised the subjects during the exercise test.

Maximal oxygen uptake (VO_2max) and carbondioxide production (VCO_2) were continuously recorded before, at the 1st min and at the 30th min of the test. Systolic, diastolic blood pressures and heart rate were measured using the conventional auscultation method. Blood samples were taken from the antecubital vein through a previously inserted catheter before the test, at the 1st min and at the 30th min of exercise to determine the plasma concentrations of AM and NO production.

Measurement of Plasma Adrenomedullin Levels

Plasma samples were placed in Supelcosil C18 columns (Cecil 100HPLC) after extraction and purification. The loaded material was eluted in a solution of 60% acetonitrile in 0.1% trifluoroacetic acid. The Adrenomedullin (1-50) (Rat) - Fluorescent EIA Kit was used as the standard to determine plasma AM levels. The variation coefficients were 2.40-3.90% for intra- and inter-assay precision, respectively (24).

Measurement of Plasma Nitrite and Nitrate Levels

The Griess reaction was used to measure plasma nitrite levels. Total nitrite (nitrite+nitrate) was measured after the conversion of nitrate to nitrite by copperized cadmium granules by a spectrophotometer at 545 nm (Ultraspec Plus, Pharmacia LKB Biochrom Ltd., England). A standard curve was established with a set of serial dilutions (10^{-8} -10^{-3} mol/l) of sodium nitrite. Results were expressed as micromoles per liter of plasma (24).

Statistical Analysis

Statistical analyses were made using Excel and SPSS version 11.0. To determine significant changes of AM and NO in the blood and arterial pressures, a one-way ANOVA was performed. In addition, correlation coefficients were calculated between variables using the accepted linear regression analysis. All results were expressed as mean±SD.

Results

Descriptive data (mean±SD) for the male athletes were age, 19.5±2.1 yr; height, 1.83±0.09 m; mass, 78.5±16.6 kg; BMI, 23.1±3.5 kg.m^{-2}. Descriptive data for the female athletes were age, 22.1±2.8 yr; height, 1.63±0.03 m; mass, 56.6±4.4 kg; BMI,

Table 1. Characteristic of the Subjects

	Female		Male	
	Athletes (n=16)	Non-athletes (n=15)	Athletes (n=14)	Non-athletes (n=15)
Age (yrs)	22.1±2.8	20.6±1.1	19.5±2.1*	21.2±1.4
Height (m)	1.63±0.03	1.63±0.04	1.83±0.09	1.77±0.07
BM (kg)	56.6±4.4	58.4±10.9	78.5±16.6	70.5±8.1
BMI (kg/m^2)	21.1±1.6	21.8±3.5	23.1±3.5	22.5±2.9

All results were expressed as mean±SD. *: p<0.02 vs male non-athlete group
BM: Body Mass, BMI: Body Mass Index

21.16±1.6 kg.m^{-2}. There were no significant differences between the female athletes and non-athletes. The only significant age difference was between the male athletes and non-athletes (Table 1).

There were no significant differences in blood pressures and heart rate between groups before exercise. The systolic and diastolic blood pressures in the female athletes showed differences from female non-athletes at the 1st min after exercise (Table 2, p<0.05). Maximal oxygen uptake (VO_2max) and carbon dioxide production (VCO_2) in female athletes were significantly higher than female non-athletes during acute exercise, respectively (Table 2, p<0.02, p<0.005).

Data for the male athletes were nitrite,13.2±2.2; nitrate, 19.9±5.5; total nitrite, 32.5±4.5. These data were significantly lower than those of the male non-athletes before and during exercise (Table 3, p<0.005). Data for the female athletes were nitrite, 13.2±2.7; nitrate, 17.8±4.8; total nitrite, 31.1±4.1. Nitric oxide products were significantly lower than those of the female non-athletes before and during exercise (Table 3, p<0.005). At the 1st min and 30th min of exrercise, there were also no significant differences in the nitric oxide products values within the groups.

Adrenomedullin or AM/BMI in the athletes (female and male) were significantly higher than in the non-athletes (female and male). However, acute exercise did not affect these differences between athletes and non-athletes. At the 1st min and 30th min of exercise, there were also no significant differences in the adrenomedullin or AM/BMI values within the groups (Figure 1, p<0.001).

However, there was a significant difference between the adrenomedullin or AM/BMI of the male-female athletes before and during exercise. These differences were not found in male and female non-athletes (Figure 2, p<0.02).

We also investigated the correlation between AM/BMI and other parameters such as blood pressures and NO production in only female-male athletes or in only female-male non-athletes. Because there were not enough subjects in the groups for correlation analysis, we did not find any relationship. However, the correlation analysis of the AM/BMI for all subjects showed a negative relationship with NO production (nitrite r=-0.275 p<0.05, nitrate r=-0.444 p<0.01 and total nitrite r=-0.498 p<0.01).

Discussion

AM is produced by a wide range of cell types, but plasma AM appears to be derived mainly from endothelial cells which are known to secrete large amounts of the peptide. Therefore, identifying factors which act on endothelial cells to modify AM secretion is of vital interest for defining blood vessel physiology and pathophysiology. In addition, a complete understanding of AM control may

Table 2. Systolic, diastolic blood pressures, heart rate, adrenomedullin levels, maximal oxygen uptake and carbon dioxide production in female-male athletes and non-athletes before exercise, at the 1st min and at the 30th min after exercise

		Female		Male	
		Athletes (n=16)	**Non-athletes (n=15)**	**Athletes (n=14)**	**Non-athletes (n=15)**
Before exercise	SBP (mmHg)	118.2±9.9	116.3±10.7	134.4±15.2	116.3±10.7
	DBP (mmHg)	75.1±9.1	79.1±8.2	80.9±7.3	79±8.2
	HR (Beats/min)	86.4±18.4	94.6±16.6	90±18	94.6±16.6
	Adrenomedullin (pmol/ml)	70±7.0*	51.6±5.0	64±6.4*	51.6±5.0
	AM/BMI (pmol.m^2. ml.$^{-1}$kg^{-1})	3.33±0.47*	2.41±0.46	2.8±0.36*	2.34±0.32
1st min	SBP (mmHg)	163.1±11.5**	128±12.1	139±20.4	127.3±27.3
	DBP (mmHg)	71.6±5.1**	76.5±7.6	71.5±9.2	70.3±12.3
	HR (Beats/min)	123±16.7	119.4±17.3	122.2±17.1	105±21.6
	Adrenomedullin (pmol/ml)	68.4±8.1*	50.4±5.8	62.7±5.6*	51.6±5.1
	AM/BMI (pmol.m^2. ml.$^{-1}$kg^1)	3.25±0.50*	2.35±0.48	2.76±0.41*	2.32±0.29
30th min	SBP (mmHg)	109.9±7.9	110.6±13.5	121.5±13	115.3±12.5
	DBP (mmHg)	72.8±6.1	74.2±7.0	73.3±7.6	76.3±7.9
	HR (Beats/min)	92.6±15	97.1±14.6	94.3±9.7	92.9±13.8
	Adrenomedullin (pmol/ml)	68.9±0.5*	50.8±3.3	61.3±5.8*	50.8±4.8
	AM/BMI (pmol.m^2. ml.$^{-1}$kg^1)	3.28±0.49*	2.37±0.42	2.69±0.38*	2.28±0.31
During exercise	VO_2max(ml.kg^1.min^1)	1.87±0.48***	1.45±0.31	2.33±0.89	2.28±0.89
	VCO_2 (ml.kg^{-1}.min^{-1})	1.63±0.53*	1.0±0.38	1.90±0.83	1.81±0.87

SP: Systolic Pressure, DP: Diastolic Pressure, HR: Heart Rate, VO_2max: Maximal Oxygen Uptake, VCO_2: Carbon Dioxide Production. All results were expressed as mean±SD. *: p<0.005 at the before, 1st min and 30th min after exercise among female athletes- female non-athletes and male athletes-male non-athletes, **: p<0.05 vs at the 1st min after exercise among female athletes- female non-athletes. ***: p<0.02 vs during exercise among female athletes-female non-athletes

Table 3. Nitrite, nitrate (micromoles/L) and total nitrite in female- male athletes and non-athletes before exercise, at the 1st min and at the 30th min after exercise

		Female		Male	
		Athletes (n=16)	**Non-athletes (n=15)**	**Athletes (n=14)**	**Non-athletes (n=15)**
Before exercise	Nitrite	13.2±2.7	15.0±2.2	13.2±2.2*	15.3±2.8
	Nitrate	17.8±4.8*	28.0±6.1	19.9±5.5*	30.2±6.3
	Total nitrite	31.1±4.1*	43.0±6.4	32.5±4.5*	45.7±6.2
1st min	Nitrite	11.4±1.3*	13.2±1.9	10.7±2.1*	15.2±2.2
	Nitrate	17.2±3.8	20.0±4.5	20.0±4.1	20.4±4.3
	Total nitrite	28.7±3.1*	33.3±3.8	30.6±2.9*	35.0±3.2
30th min	Nitrite	10.4±1.5*	12.6±2.1	9.3±1.7*	11.7±2.3
	Nitrate	19.9±4.5*	25.9±5.5	19.2±4.7*	27.7±6.6
	Total nitrite	30.5±3.4*	38.5±4.4	28.6±4.7*	39.7±6.7

All results were expressed as mean±SD. *: p<0.005 before, at the 1st min and 30th min after exercise among female athletes with female non-athletes and male athletes with male non-athletes

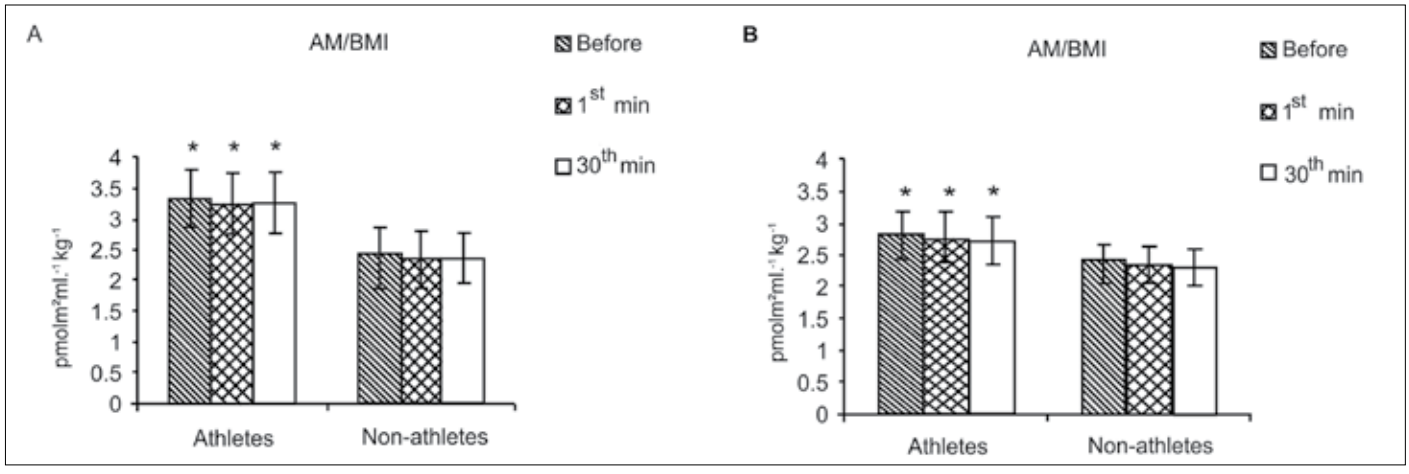

Figure 1. AM/BMI in female (A) and male athletes (B) before exercise, at the 1st min and at the 30th min after exercise
AM: Adrenomedullin, BMI: Body Mass Index. All results were expressed as mean±SD. *: p<0.001 vs non-athletes

clarify paracrine and autocrine processes which contribute to vascular structure, function and dysfunction.

The main finding of the present study is that regular physical activity resulted in a significant increase in the plasma AM concentration of young athletes compared with that of non-athletes. Without taking gender differences into consideration, all athletes have higher AM levels compared to non-athletes. It is interesting that immediately after, and half an hour after maximal exercise load, plasma AM concentration did not change in female and male athletes. This finding contradicts previously reported data indicating that intensive dynamic exercise may sitmulate AM release (16). Consistent with the results of this study, Krzeminski et al. (23) suggested that maximal exercise inhibits AM secretion in young healthy men.

This may suggest that increased peripheral vascular resistance and expanded plasma volume are important stimulants of AM production (13, 22, 23, 25). Exhaustive exercise decreases both peripheral resistance and plasma volume (26). It seems likely that vasodilation induced by local chemical changes in working muscles, as well as reduction in plasma volume, affect AM production and secretion during this acute type of exercise. The subjects participating in the present study were young and tolerated greater workloads.

The present study did not find any relationship between AM values and mean, systolic, diastolic pressures or heart rate during either regular physical activity or in acute exercise. Krzeminski et al. (23) suggested that the exercise-induced quantity of AM released into circulation is too small to directly affect blood pressure so it may instead reflect increased activity as an autocrine or a paracrine factor. In the present study, regular physical activity induced a significant increase in plasma AM concentration in female athletes compared with male athletes. However, this difference between female-male athletes was not demonstrated in non-athlete subjects.

It has been reported that neither oestradiol nor testosterone influenced adrenomedullin mRNA levels in cultured rat aortic endothelial cells (27). On the other hand, both testosterone and oestradiol were shown to increase immunoreactive adrenomedullin secretion from rat aortic endothelial cells in culture (28). Pearson et al. (29)

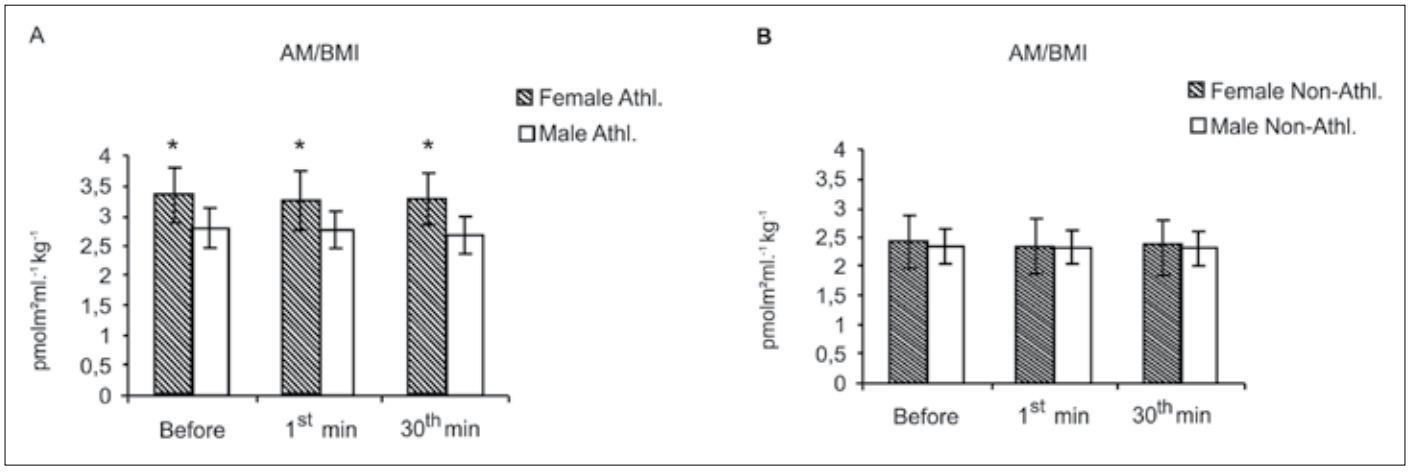

Figure 2. Differences of AM/BMI between female and male athletes (A) and female and male non-athletes subjects (B) before exercise, at the 1st min and at the 30th min after exercise. All results were expressed as mean±SD. *: p<0.02 vs male athletes

demonstrated that AM mRNA expression was significantly increased by testosterone, and there was also a tendency for an increase in AM mRNA expression, which occurred when cells were incubated with angiotensin-II. The mechanism responsible for increased plasma AM levels in female athletes may be due to hormonal changes brought about by increased training stress. An exaggerated increase in fasting cortisol with an increase in training stress in female compared to male athletes was found (30, 31), but in this study, we did not examine the cortisol level in female subjects. A strong positive correlation between the exercise-induced increases in plasma AM and noradrenalin (NA) was observed between AM and other hormones such as plasma renin and atrial natriuretic peptide (ANP) in healthy men. However, the relationship between hormones and plasma AM in healthy men during prolonged physical activity was not investigated separately in female subjects. Future studies should aim to address this disparity, specifically in the clinical population. Krzeminski et al. (21) observed a strong positive correlation between plasma AM and NA concentrations as well as between the exercise-induced increases in plasma AM and NA in healthy young men. We speculate that the adrenergic effect in female athletes may be higher than in male athletes, therefore the increase in plasma NA concentration may contribute to AM response to prolonged dynamic exercise.

The vascular actions of AM exert endothelium-dependent and endothelium-independent vasodilation. AM was found to stimulate phospholipase C activation and inositol 1,4,5- triphosphate formation, resulting in an elevation of the intracellular Ca^{+2} level and activation of NO synthase (32). On the other hand, endothelium-independent vasodilatation by AM suggests an increase in intracellular cyclic AMP (cAMP) level, a decrease in the Ca^{+2} concentration, and the activation of K^{+} channels in vascular smooth muscle cells (32). Hattori et al. (33) clearly demonstrated that AM changes nitric oxide synthetase (iNOS) expression and results in an increment in NO levels.

As a putative compensatory factor, AM is able to buffer the pressure action as a stimulator of NO synthesis. The present study demonstrated that regular physical activity induced a significant decrease in NO production in female-male athletes. There was a negative relationship between AM values and NO production. NO production decreased after acute exercise in female-male non-athletes, but not in female-male athletes. At 30 min. after exercise, NO production rose to normal levels.

We thought that overly expressed AM augmented collateral development in response to regular physical activity. This suggests that, in regular physical activity, the effect of AM was exerted through NO release by activation of eNOS. In fact, recent studies indicate that a large amount of NO may promote angiogenesis because most angiogenic factors, including VEGF, promote NO release from endothelial cells (34). Blood flow recovery in response to prolonged physical activity may not induce an additional increase in the NO synthesis.

The reason for the discrepancy between results obtained in previous studies and this study can be due to age, gender, weight and exercise program differences of the participating subjects.

In this study, the effect of regular physical activity and acute exercise on AM concentration was examined in female-male subjects. Athletes had higher AM levels than non-athletes. However, acute exercise did not induce a corresponding change in plasma AM levels in subjects. In female athletes, AM levels were higher than those in male athletes. Athletes had lower NO production levels than non-athletes. These findings suggest that AM is sensitive to regular physical activity, but is not sensitive to acute exercise. AM was affected by gender differences, and it was related to NO production

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Conflict of interest
No conflict of interest was declared by the authors.

Authors' contributions: Conceived and designed the experiments: ND. Performed the experiments: ND, MY, KO. Analyzed the data: ND. Wrote the paper: ND, KO. All authors read and approved the final manuscript.

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