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EFFECT OF ANABOLIC-ANDROGENIC STEROIDS ON THE ACTIVITY OF RENNIN-ANGIOTENSIN-ALDOSTERONE SYSTEM, ECHOCARDIOGRAPHY PARAMETERS AND ON THE BODY MASS IN BODY BUILDERS

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Abstract. This study was performed in groups of body builders: Group I (18 subjects) in whose metabolites of anabolic-androgenic-steroids (AAS) were detected in urine, and Group II (22 subjects) where no AAS were found in urine. Echocardiography parameters, aldosterone, rennin activity in plasma and AAS metabolites in urine were measured. The results of both groups of body builders were compared with those obtained in 30 cyclists and 26 rowers (no AAS detected). It was found that plasma aldosterone level in body builders correlated well with the heart echocardiography parameters, body mass index (BMI) and with the activity of serum angiotensin converting enzyme (ACE). No such relationship existed in tested rowers and cyclists. These groups were characterised by statistically significant relation between aldosterone level in blood plasma and the rennin plasma activity (ARO) which, on the other hand, was not found in the groups of body builders. The correlation between aldosterone level and the rennin blood plasma activity in cyclists and rowers might be an effect of strong stimulation of RAAS (higher in cyclists than rowers) resulting from the intense physical effort. Lack of such relation in body builders might be caused by a stronger tissue activation of the RAAS modifying aldosterone activity and bringing in result an increase in body mass and left ventricle hypertrophy. Results of the study suggest, therefore, that supra-physiological doses of AAS could enhance tissue activity of the rennin-angiotensin-aldosterone system (RAAS) what, with coincidence, of other pathogenic factors (i.e.: inflammatory states, toxic substances, injuries, great stress) may play an important role in the process of pathogenesis of the cardiovascular disorders leading to a sudden heart attacks.

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Introduction

Several clinical trials showed that application of anabolic-androgenic steroids (AAS) in the normal, pharmacological doses has an advantageous effect in many diseases and is completely safe during therapy [16]. On the other hand, the long-lasting non medical intake of large doses of steroids (described as a supra-physiological or mega doses) by men and women attending fitness clubs can seriously harm their health [3,8,19,22,26,28,32,34]. Although effects of application of the supra-physiological doses of AAS by athletes, for the purpose of muscle mass growth and better results in force disciplines of sport were confirmed in recent years [1] but the physiological mechanism of this phenomenon remains unclear. A long term of AAS intake may bring various side effects resulting in serious health damages [3,12,13,22,24,28]. Overdoses of AAS causes cardiovascular disorders such as hypertrophy of the left ventricle of the heart, arterial hypertension, cardiac arrhythmia, blood clotting, coronary blood flow disability, myocardium inflammation, acute coronary inefficiency, cardiac infractions, arterial sclerosis, circulatory failure and heart attacks which may end of sudden death in people willing to achieve a sport success by any costs [8,12,17,18,19,34]. Overdoses of AAS can also trigger some mental instability in the form of a maniac-depressive states expressed by uncontrolled aggression or deep depression associated with some suicidal inclinations [10,18,24,26,34].

On the other hand, despite of the mass application of AAS by youngsters and adults, only relatively small number of the mentioned health disorders was noted, especially under controlled circumstances [1]. As a consequence, there are some opinions in medical society that those casuistic cases might be exaggerated when side effects (cardiovascular in particular) of large doses of AAS are considered [8,13,29,32,33].

In pathogenesis of cardiovascular diseases (especially of the left ventricle hypertrophy, vascular disturbances and cardiac infractions) some attention was focused on the role of rennin-angiotensin-aldosterone system (RAAS), specifically on its important effectors angiotensin II and aldosterone [6,7,9,23,31]. Beyond the well known hormonal or circular activity of the above system regulating the arterial blood pressure and water-electrolyte balance, the recent publication show that all basic elements of RAAS are synthesized in many organs e.g.: heart muscle, skeletal

muscles, vessels endothelium, brain, kidneys and reproductive organs [5,20,30,31,36].

It should be noted that tissue synthesis of aldosterone is enhanced in overgrown organs that is also in heart muscle and skeletal muscles [5,7,20,21,23,29,36]. The organic or tissue RAAS exhibits a local activity intracellular, on cells sphere or inside of the neighbouring cells. The system functions through the stimulation of the cascade of tissue mediators and growth factors which can elicit a hypertrophy of in skeletal muscles, heart muscle or vessels smooth muscles, or the reverse can cause the muscles atrophy [23,31,36]. The tissue activity of the rennin-angiotensin-aldosterone system is a crucial element in regulation of the cardiovascular system under pathological conditions as well as during the adaptation process adjusting the cardiovascular system to the intense physical efforts performed by athletes [5,6,7,9,21,30,35].

Our previous study revealed an increased aldosterone level in blood plasma in subjects currently using AAS and in those who recently ceased using the AAS [3]. The question therefore raised, whether the organism's response to overdoses of AAS elicit both, the "profitable" (skeletal muscles mass increase) and unfavourable (causing morbid symptoms) effects by changed activity of the rennin-angiotensin-aldosterone system (RAAS) [3].

The aim of this study was to investigate possible relationship between the left ventricle hypertrophy of the heart, echocardiography parameters, body mass and levels of plasma markers of RAAS activity in subjects using supra-physiological doses of anabolic-androgenic steroids (body builders) and in sportsmen not using AAS (cyclists and rowers).

Material and Methods

The study was performed on 40 body builders, amateurs or former athletes. Informed, written consent of the subjects was obtained and experiments were accepted by the Ethics Committee of the Institute of Sport.

The body builders were divided into two sub-groups. The first, determined as "positive" consisted of 18 subjects in whose anabolic-androgen steroid metabolites were present in urine samples. The second group, "negative" included 22 subjects whose urine samples did not contain any AAS metabolites.

Table 1 and Table 2 present basic characteristics of the subjects including age, years of AAS application, number of cycles of the AAS application, weeks of AAS intake in the last cycle, type and amount of recently used medicine and AAS metabolites found in urine. Table 1 shows data of 9 body builders who declared

current taking of AAS ("on cycle") while Table 2 the data of 9 body builders in whose AAS metabolites were detected in urine samples (mainly nandrolone) though they claimed not taking the steroids at least in the period of 1-12 months.

Table 1
Characteristic of body builders declaring current intake of SAA ("on cycle")

No	Age (years)	Years of AAS applica-tion	Weeks of intake during cycle	Amount of cycles in life	AAS metabolites detected in urine	Doses of drugs consumed during the last cycle (mg)
1	46	17	6	51	Metenolone, Stanozolol, T/Et* - 33.2	Metandienone, 610 mg, Nandrolone, 600 mg, Testosterone, 7000 mg
2	33	3	12	7	19-NA**-547 ng/ml Metenolone I, II	Metandienone, 550 mg, Nandrolone, 1500 mg Testosterone, 875 mg, Clenbuterol, 720 mg HCG, 24 u, Insulin, 60 u
3	23	2	8	3	19-NA - 221 ng/ml	Metandienone, 1000 mg, Nandrolone, 1800 mg, Omnandren, 3500 mg, Gonadotropin, 6000 u
4	30	11	4	4	19-NA - 227 ng/ml Epimetendiol; Stanozolol, Oxandrolone, T/Et - 76	Oxandrolone, 850 mg, Boldenone, 800 mg, Vinstrol, 1600 mg
5	33	5	8	6	Boldenone II, Metenolone I,II	Nandrolone, 2250 mg Omnandrene, 2000 mg Clenbuterol, HCG
6	29	8	12	6	19-NA – 255.6 ng/ml Epimetendiol, 3'stanazolol Oxandrolone T/Et – 75.6	Metandienone, 1000 mg Nandrolone, 1000 mg Omnandren, 3000 mg

7	29	7	8	12	19-NA – 56.5 ng/ml	Metandienone, 1250 mg Primabolan, 1200 mg Testosterone, 1500 mg
8	31	10	6	30	Metenolone I, II; T/Et - 41, 19-NA - 7 ng/ml DHT***.	Primobolan, 400 mg Sustanon, 2000 mg HGH, 84 u
9	28	1,5	1	7	3',4'Beta Stanozolol	Metandienone, 1505 mg, Vinstrol, 1000 mg

*T/ET - ratio of testosterone to epitestosterone; **19-NA - 19 norandrosterone; ***DHT=dihydrotestosterone

Table 2.
Characteristic of the body builders declaring not taking AAS during the time of experiments (''off cycle''), though they urine samples still contained some steroid metabolites

No	Age (years)	Years of AAS applica-tion	Period in cessation of AAS application (months)	Amount of weeks during the cycle	Amount of cycles in life	AAS metabolites detected in urine	Doses of drugs consumed during the last cycle (mg)
10	23	4	3	7	4	Metenolone I, II	Metandienone, 1050 mg Oxandrolone, 612 mg HCG, 6000 u
11	23	2	3	7	3	Metandienone, 19-NA, 43 ng/ml	Metandienone, 1470 mg Nandrolone, 350 mg Testosterone, 9000 mg
12	20	3	1	5	5	19-NA, 325 ng/ml	Metandienone, 1500 mg Nandrolone, 600 mg Testosterone, 6500 mg HCG, 1000 u
13	24	3	3	8	4	19-NA, 22 ng/ml	Nandrolone, 1000 mg Vinstrol, 800 mg
14	19	3	1	12	1	19-NA, 18.5 ng/ml THC, 13.5 ng/ml	Metandienone, 1000 mg Nandrolone, 1250 mg Testosterone, 2500 mg Vinstrol, 500 mg

15	29	7	2	6	7	19-NA, 56.5 ng/ml	Metandienone, 1250 mg Primabolan, 1200 mg Testosterone, 1500 mg
16	34	10	1	8	6t	19-NA, 34.3 ng/ml	Metandienone, 1500 mg Nandrolone, 250 mg Testosterone, 2000 mg Metenolone, 750 mg
17	16	1	1	7	1	19-NA, 34.9 ng/ml	Metandienone, 1000 mg Omnandren, 1750 mg
18	30	11	2,5	6	36	19-NA, 50 ng/ml, 3'OH Stanozolol.	Oxandrolon,850 mg Boldenon, 800 mg Vinstrol, 1600 mg

Among 18 tested subjects, the nandrolone (19-nor-androsterone) concentration in urine exceeding the level of 2ng/ml (for men) was found in 8 samples. Next 6 samples contained both nandrolone and other steroid metabolites. In last 4 samples various anabolic steroid metabolites were found.

Results of the study performed in body builders were compared with data attained from 30 road cyclists and 26 rowers. None of the above mentioned athletes showed any presence of the AAS metabolites in urine nor the steroid profile disturbances.

Each subject filled up the questionnaire concerning the AAS type and intake history and observed health disorders. Next, the subject was medically checked including ECG recordings (Marquette Hellige).

The echocardiography examination was conducted by the ACUSON apparatus. The evaluation of measurements was made always by the same person. The left ventricle mass (LVM) of heart was counted according to the formula of Devereux:

$$\mathbf{0.8[1.04(IVSd+LVdD+PWd)^3-LVdD^3]+0.6\ g.}$$

Other indices were also calculated: LVM in transformation to subjects height in cm taking the border value of >1.7 g/cm or 170 g/m [35]; heart mass index (g/m^2) describing the left ventricle mass to body surface area (MIM) taking the proper border value up to 143 g/m^2 [14]; left ventricle dimension of diastole (LVdD) (cm); inter-ventricular septum diastole dimension (IVSd) (cm) and left ventricle posterior wall dimension of diastole (PWd) accepting the border value of 1.2-1.3 cm [35].

After 12 h fasting from each subject the blood sample from cubital vein was taken into two separate tubes. The first tube, filled with a sodium versenate was designated for aldosterone and rennin plasma activity (ARO) measurements. It was whirled in chilled centrifuge and kept in 80°C for further analyses. In the second tube the blood for a clot for biochemical and hormonal analyses as well as for determination of angiotensin converting enzyme (ACE) activity was collected.

All subjects were asked to collect a 24-hour urine sample, used for detection of anabolic steroid metabolites and for the evaluation excretion of sodium and potassium. Aldosterone level in plasma was estimated by the method of Ignatowska-Świtalska adapted for the blood plasma assay [11]. The aldosterone in plasma was extracted with dichloromethane and determined in duplicates with the RIA method using the aldosterone antibodies of SIGMA #A3793, marked by tritium of aldosterone (ELKABE-Amersham) and standard of aldosterone (Peninsula). Applied antibodies showed lower than 0.001% cross reaction with the cortisone, corticosterone and dezoxycorticosterone. The coefficients of the method variability was 8% for intra-serial and 12% for inter-serial [11]. Plasma rennin activity was determined with the RIA method (Immunotech kit Cat#3518). The angiotensin converting enzyme (ACE) activity was measured according to the Liberman method [15].

Statistical Analyses

The mean values (±standard deviation) of the results in respective groups were calculated with the ANOVA test by STATISTICA StatSoft Programme v6. Because of non-parametric distribution of the data the statistical significance of differences were estimated with Kruskal-Willis tests for independent groups. The correlation coefficients for intra groups were marked with the non-parametric rank test of Spearman, accepting the significance level at $p<0.05$.

Results

Table 3 presents the mean values (±SD) of results obtained in 40 body builders, 26 rowers and 30 cyclists. The statistical analysis showed a significant differences regarding the anthropometrical parameters such as age, body mass, height, body mass index (BMI) and body surface area (BSA). The group of body builders differed from rowers and cyclists with age, body mass, BIM and BSA.

Table 3
Biophysical characteristics of the subjects and echocardiography parameters of the left ventricle of the heart, rennin plasma activity (ARO), angiotensine converting enzyme (ACE) activity and levels of plasma aldosterone (ALDO) in groups of: culturists, cyclists and rowers (ANOVA test: means ± SE)

	1. Body builders	2. Rowers	3. Cyclists	Statistical significance		
Number of subjects	40	26	30	1 vs 2	1 vs 3	2 vs 3
Age (years)	29.2±1.3	20.7±1.1	26.1±0.6	***	***	***
Body mass (kg)	92.7±1.8	86.2±1.7	74.8±1.1	***	***	**
Height (cm)	176.4±0.9	189.2±1.3	181.3±1.2	**	NS	NS
Body mass index BMI (kg/ m^2)	29.8±0.5	23.9±0.3	22.7±0.2	***	**	NS
Body surface area BSA (m^2)	2.03±0.02	2.13±0.02	1.94±0.02	*	***	**
Left ventricle mass - LK (g)	259.4±8.8	266.2±8.6	262.7±8.8	*	NS	NS
Left ventricle mass/height (g/cm)	1.47±0.04	1.4±0.04	1.45±0.04	***	*	NS
MIM (g/m^2)	122.7±3.2	125.1±3.4	135.2±4.3	*	NS	*
LVdD (cm)	5.48±0.06	5.57±0.05	5.49±0.06	NS	NS	NS
IVSd (cm)	1.15±0.012	1.55±0.02	1.17±0.02	**	NS	NS
PWd (cm)	1.147±0.014	1.146±0.015	1.157±0.02	*	NS	NS
ARO u/ml/h	2.37±0.27	1.04±0.15	1.66±0.2	***	***	**
ACE (mU/ml)	30.2±1.3	29.5±1.5	25.8±1.2	*	***	NS
ALDO (ng/dl)	9.95±0.8	9.5±1.1	13.5±1.3	***	NS	**
ALDO/ARO	7.0±1.0	12.4±1.3	10.0±1.0	NS	NS	NS
Systolic blood pressure (mm Hg)	127.5±1.6	125.4±1.4	112.5±2.2	***	***	**
Diastolic blood pressure (mmHg)	81.2±1.1	76.1±0.9	71±1.2	***	***	NS

Significance of average differences in groups evaluated with the test of Kruskal-Willis; p value for repeated comparisons;
*p<0.05; **p<0.01; ***p<0.001; NS - no significant
Abbreviations:
MIM – heart mass index (g/m^2) = left ventricle mass / body scope area,

LVdD – diastolic dimension of the left ventricle,
IVSd – diastolic dimension of the ventricular septum,
PWD – diastolic dimension of the left ventricle posterior wall,
ARO – plasma renin activity
ACE – conversionary enzyme activity,
ALDO - aldosterone

The left ventricle mass (g), heart muscle mass index (MIM) (g/m^2), diastolic dimension of the inter-ventricular septum (IVSd) (cm) were significantly greater in rowers than in body builders. In contrast, the left ventricle mass/height index (g/cm) and the dimension of the left ventricle posterior wall during diastole (PWd) (cm) were greater in body builders than in rowers. No significant differences were found in the echocardiography parameters between body builders and cyclists with the exception of the left ventricle mass index (g/cm) which was statistically higher in body builders. In the echocardiography parameters the only difference found between rowers and cyclists was the MIM values ($p<0.043$). The diastolic dimension of the left ventricle (LVdD) (cm) did not differ significantly in all tested groups.

The rennin plasma activity (ARO) differed significantly between the groups of subjects. The greatest values of ARO were found in body builders but the ARO was lower in rowers than in cyclists ($p<0.008$). The ACE activity was significantly greater in body builders than in cyclists ($p<0.002$) and rowers ($p<0.0002$). Mean values of aldosterone level in plasma differed significantly between body builders and rowers ($p<0.0003$).

The systolic (RRs) and diastolic (RRd) arterial blood pressures were clinically accepted limits for all groups of subjects. However, the mean values of (RRs) were significantly greater in the group of body builders comparing with rowers and cyclists. Also the diastolic blood pressure (RRd) was greater in body builders.

Important differences between groups of subjects were found during the intra-group analyses regarding aldosterone in blood plasma, anthropometrical parameters and the left ventricle of heart dimensions as well as of the rennin plasma activity. The results of the analyses are presented in Table 4. In body builders some positive correlation coefficients were found between aldosterone level and the following echocardiography parameters: left ventricle mass, left ventricle mass index/height, diastolic dimension of the left ventricle septum (IVSd) as well as the body mass index (BMI), aldosterone level and ACE activity in the blood serum. Such relationships were not found for rowers and cyclists. Instead, a significant correlations were found for aldosterone levels in plasma and rennin plasma

activities were found in rowers and cyclists. Alike correlations did not occur in the group of body builders.

ECG did not revealed any significant deviations fro clinical norm in all groups of subjects.

Table 4
Correlations of rank order, according to Spearman, between levels of aldosterone in blood plasma (ALDO) and anthropomorphic data, echocardiography parameters of the left ventricle of heart, ARO and ACE activities and systolic and diastolic blood pressures (ANOVA test)

Tested groups	Body builders	Rowers	Cyclists
Number of subjects	40	26	30
Aldosterone in plasma (ng/dl)	ALDO	ALDO	ALDO
Body mass (kg)	0.307 *	-0.07 (NS)	-0.018 (NS)
Height (cm)	0.014 (NS)	0.08 (NS)	-0.07 (NS)
Body mass index BMI (kg/m^2)	0.317 *	-0.15 (NS)	0.05 (NS)
Body surface area BSA (m^2)	0.27 (NS)	-0.04 (NS)	0.18 (NS)
Left ventricle mass ($g.m^{-1}$)	0.33 *	-0.19 (NS)	0.14 (NS)
Left ventricle mass/height ($g.m^{-1}/cm$)	0.33 *	-0.17 (NS)	0.13 (NS)
MIM ($g.m^{-1}/m^2$)	0.22 (NS)	-0.05 (NS)	0.03 (NS)
LVdD (cm)	0.31 *	-0.21 (NS)	0.26 (NS)
IVSd (cm)	0.33 *	0.009 (NS)	-0.0004 (NS)
PWd (cm)	0.25 (NS)	0.07 (NS)	0.12 (NS)
ARO (ng/ml/h)	0.17 (NS)	0.55 **	0.68 **
ACE (mU/ml)	0.32 *	0.09 (NS)	-0.11 (NS)
ALDO/ARO index	0.29 (NS)	0.11 (NS)	0.07 (NS)
Systolic blood pressure RRs (mmHg)	-0.12 (NS)	0.29 (NS)	0.12 (NS)
Diastolic blood pressure RRd (mmHg)	-0.15 (NS)	-0.09 (NS)	-0.06 (NS)

R - correlation coefficients significant at: *$p<0.05$; **$p<0.01$; NS – No significant
Abbreviations: see Table 3.

Discussion

Recent clinical and experimental studies proved the involvement of increased activity of RAAS in pathogenesis of serious cardiovascular disturbances by stimulation of heart muscle fibrosis (deposition of collagen type I and II) [25], handicap diastolic and systolic heart function, left ventricle hypertrophy and blood vessels fibrosis leading to cardiovascular inefficiency and sudden cardiac death [5,6,7,27,30,36]. There was also reported that aldosterone can influence cardiac arrhythmia and disturb coagulation properties of blood [7,8,25,35,42].

Aldosterone acts directly on the cardiovascular system influences without elevation of blood pressure [6,27,31,36]. That is probably why, the increased aldosterone level is regarded as an independent factor of the enlarged risk in cardiovascular diseases [27].

Increased level of tissue aldosterone stimulates expression of converting mRNA enzyme (ACE) causing an elevated synthesis of angiotensin II [36]. This mechanism seems be confirmed by the results of the present work showing a significant relationship between aldosterone level in blood plasma and ACE activity in body builders.

A positive feed-back mechanism based on angiotensin II and aldosterone can be involved in development of some cardiovascular diseases [36]. The angiotensin II, through activation of AT1 receptors, enlarges aldosterone synthesis which trigger tissue activity of ACE leading to further increase of the angiotensin II synthesis. Aldosterone also increases sensitivity of AT1 receptors enhancing effects of angiotensin II. Aldosterone increases the gene expression and modifies blood vessels endothelium what elicit spastic action of coronary vessels, ischaemic state and possible cardiac infractions [7,8,27,30,36]. Casuistic cases concerning abuse of AAS and described in bibliography indicate some role of the above mentioned mechanism in development of cardiovascular diseases [6,19,22,36].

In the study of Cubero *et al.* [4] aldosterone level measured in the group of 40 cyclists was similar to that observed in our cyclists. Similarly, in both discussed works no relationship was found between aldosterone level in blood plasma and heart dimension. These data suggest that aldosterone level has not significant influence on physiological hypertrophy of heart muscle (athlete's heart) in cyclist not using AAS.

However, the significant relationship between aldosterone concentration in blood plasma and the left ventricle mass of heart in body builders using large doses of AAS would indicate that the level of activation of rennin-angiotensin-aldosterone system could play an important role in pathogenesis of cardiovascular diseases. This

hypothesis can be supported by a histopathological examination of a heart muscle with hypertrophy (530 g) of a 21 years old weight lifter who died suddenly [2]. He was taking the AAS (testosterone and nandrolone) during last few months before his death. The examination showed advanced interstitial fibrosis of both ventricles, atriums walls and coronary vessels. Similar changes were observed under aldosterone excess in experiments performed on animals [2].

Nieminen *et al.* [22] described some pathological changes of the cardiovascular system in 4 young weight lifters using large doses of anabolic steroids and practising an intensive force training. The all 4 sportsmen had the heart muscle hypertrophy, 2 of them showed cardiac insufficiency and in 1 subjects massive thrombosis changes in both heart ventricles were found. Similar cardiovascular changes in 2 body builders were reported by McCarthy *et al.* [17].

Pathogenesis of overgrowth of skeletal muscles and heart muscle hypertrophy in subjects taking large doses of AAS is a complex process. It consist of many factors including the insulin-like growth factor 1 (ILGF1) and tissue growth factor 1 (TGFβ1) [16,29,36]. However, participation of angiotensin II and aldosterone in this process is essential [9].

Assuming the border values of the left ventricle mass (transferred into height cm) over 1.7 g/cm [35], the heart mass index (left ventricle mass/body scope area – MIM g/m^2) over 143 g/m^2 [14] and diastolic dimension of the left ventricle posterior wall (PWd) (cm) between 1.2 and 1.3 cm [35] it was found that 4 body builders, 2 rowers and 9 cyclists exceeded those limits.

The highest values of the above indices were recorded in one body builder, examined in 4th week of the cycle of AAS intake: MLK = 452 g; MLK/cm =2.58 g; MIM = 196 g/m^2; PWd = 1.4 cm. The echocardiography measurement repeated after 2 months of brake in AAS intake revealed the above indices diminished for about 16%, despite of the constant presence of AAS metabolites in urine samples.

The cardiological evaluation of both groups of body builders using the AAS and former users showed normal haemodynamic efficiency of the circulatory system, without pathological changes.

Conclusions

- This study demonstrated a significant correlation between aldosterone level in the blood plasma and mass of the left ventricle of heart, other echocardiography parameters, body mass index (BMI) and ACE activity in the blood serum of body builders. Rowers and cyclists showed a relationship between aldosterone level in blood plasma and rennin plasma activity (ARO).

- Obtained results suggest that the left ventricle hypertrophy and body mass increase in men taking large doses of AAS may be an effect of strong activation of tissue rennin-angiotensin-aldosterone system, what in connection with other pathogenic factors (inflammatory states, toxic substances, injuries or strong stress) may play an important role in pathogenesis of cardiovascular diseases.

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