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Supplementation with L-arginine does not influence arterial blood pressure in healthy people: a randomized, double blind, trial

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Abstract. – *Background and Objectives:* **It cannot be excluded that supplementation with L-arginine, by improving function of endothelium and hypotensive effect, can be advantegeous in prevention of cardiovascular diseases in healthy people. However, reports about hypotensive effect of L-arginine in healthy people are unclear. Moreover, no research including ambulatory blood pressure measurement (ABPM) has been conducted so far. Therefore, the aim of our study was to show if 4-week supplementation of healthy people with L-arginine influences blood pressure measured with ABPM.**

Materials and Methods: **The study was carried out on 19 healthy people randomized to 6 g/24-hour, 12 g/24-hours of L-arginine or placebo. ABPM was carried out 4 times: before randomization, after 2 and 4 weeks of supplementation and 2 weeks after finishing supplementation.**

Results: **It was found that 4 weeks of supplementation of healthy people with L-arginine (6 or 12 g/24-hour) led to nonsignificant decrease of systolic and diastolic blood pressure; the decrease was greater during night.**

Conclusion: **These findings showed that supplementation with L-arginine is not necessarily advantageous in healthy people.**

Key Words:

ABPM, L-arginine, Supplementation.

Introduction

Improvement of endothelial function by L-arginine suggests that the supplementation with this amino acid may be beneficial in the treatment and prevention of cardiovascular diseases[1-3]. There are numerous studies focusing on essential hypertension, pulmonary hypertension, atherosclerosis of lower limbs, hypercholesteremia, stable angina, diabetes mellitus[4-7]. Supplementation with L-arginine may be advantageous also in healthy people[8] by preventing primary cardiovascular diseases[9,10].

In studies conducted so far the influence of oral and intravenous supplementation with L-arginine on blood pressure of healthy people was estimated. Yet, no research including the ambulatory blood pressure measurement (ABPM) has been conducted[11-14].

Therefore, the aim of this study was to examine whether 4-week supplementation with L-arginine influences the blood pressure in 24-hour measurement (ABPM) in healthy people and to evaluate the safety of application of L-arginine in a randomized study with double blind trial and placebo.

Materials and Methods

The protocol of study was accepted by local Bioethical Committee, Karol Marcinkowski University of Medical Sciences (permission number 275/04). Written consent for participation in the investigation was obtained from all volunteers.

The studied group consisted of 19 healthy people (9 women, 10 men; age: 37.9±8.03 years). 8 subjects (4 men, 4 women) had positive family history (one of parents or siblings suffered arterial hypertension). A prospective randomized study with double blind trial has been conducted for 6 weeks. The subjects were randomized to

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take L-arginine (3 × 2 g or 3 × 4 g) or placebo 3 times per 24-hour for 4 weeks. Medical interview, physical examination, basic biochemical examination and ambulatory blood pressure measurement (ABPM) was carried out during the first visit. Repeated ABPM was carried out after 2 and 4 weeks of L-arginine supplementation and 2 weeks after finishing supplementation (6 weeks after beginning of the study).

ABPM-04 device (Meditech Ltd., Budapest, Hungary) validated by AAMI and BHS (B/B class)[15] was used for ambulatory blood pressure measurement. Measurement of blood pressure began between 8:00 and 10:00 and stopped after 24-hour. The frequency of measurements was 1 per 15 minutes during day and 1 per 30 minutes during night. The periods were fixed arbitrarily: day – 7:00-22:59, night – 23:00-6:59. Obtained data was processed with computer software.

Statistical Analysis

Statistical analysis included 24-hour records which met following criteria: beginning of the record between 8:00 and 10:00, at least 70% of valid measurement per 24-hour (including at least 7 measurements from the night). In the case of not meeting these criteria, measurements were repeated. Additional parameters were estimated on the basis of ABPM: systolic blood pressure for 24-hour measurement (SBP_{24h}), diastolic blood pressure for 24-hour measurement (DBP_{24h}), systolic blood pressure for day measurement (SBP_d), diastolic blood pressure for day measurement (DBP_d), systolic blood pressure for night measurement (SBP_n), diastolic blood pressure for night measurement (DBP_n), average blood pressure for 24-hour measurement (MAP_{24h}).

MS Excel 2000 and Statistica 7 PL software were used to elaborate data and for statistical analysis. As the level of statistical significance was $p < 0.05$.

Results

Clinical characteristic of studied groups is presented in Table I while the results of laboratory examinations of studied subgroups are presented in Table II. No statistically significant difference among the subgroups was found concerning clinical parameters and blood morphology. Statistically significant differences concerning the concentration of triglycerides and urea were found among all subgroups. Moreover, the subgroup taking placebo differed significantly from group treated with 2 g of L-arginine in average concentration of cholesterol and LDL ($p<0.05$). No statistically significant differences were found concerning the rest of biochemical parameters.

Average values of systolic (SBP) and diastolic (DBP) blood pressure for 24-hour, day and night measurements in all subgroups are presented in Figures 1 to 6. Average values of blood pressure measured 24-hour are presented in Figure 7. Characteristics of average values of systolic (SBP) and diastolic (DBP) blood pressure for 24-hour, day and night measurements in all subgroups are presented in Tables III and IV. The characteristic of average blood pressure for 24-hour measurement is presented in Table V.

Over the period of study a decrease of average values of systolic blood pressure was found in both groups supplemented with L-arginine. However, the decrease was not statistically significant (Figure 1, Table III). No statistically significant differences were found among studied groups concerning initial and end values of DBP measured 24-hour (Figure 2, Table IV). There was a declining tendency in SBP values from the day measurement in patients supplemented with L-arginine, yet observed decrease was not statistically significant (Figure 3, Table III). No statistically significant differences were found among studied groups concerning initial and end values of DBP measured during day (Figure 4, Table IV). There was a clear declining tendency in SBP measured during night between 0 and 4 visit, especially for the subgroup

Table I. Clinical characteristic of studied subjects with division to subgroups. Group I – patients supplemented with L-arginine 6 g/24-hour; group II – L-arginine 12 g/24-hour; group III – patients taking placebo.

Group	N (M/W)	Age (years)	Body mass (kg)	Height (cm)	BMI (kg/m^2)
I (3 × 2 g)	7 (4/3)	37.7 ± 10.3	73.3 ± 13.6	174 ± 5.94	23.9 ± 2.99
II (3 × 4 g)	6 (3/3)	40.7 ± 7.58	84.7 ± 16.0	178 ± 9.09	26.7 ± 3.4
III (placebo)	6 (3/3)	35.3 ± 5.43	76.0 ± 19.1	180 ± 10.9	23.3 ± 3.48

Table II. The results of laboratory examinations of studied subgroups.

	Group I (3x 2 g, n =7)			Group II (3 x 4 g, n = 6)			Group III (placebo, n=6)		
	Min	Max	M ± SD	Min	Max	M ± SD	Min	Max	M ± SD
Hgb (mmol/l)	8.00	10.10	9.13 ± 0.69	7.90	10.10	9.10 ± 0.92	8.90	10.20	9.53 ± 0.51
RBC ($\times 10^{12}$/l)	3.90	5.45	4.74 ± 0.59	4.35	5.60	5.23 ± 0.46	4.57	5.45	4.96 ± 0.51
WBC ($\times 10^{9}$/l)	5.00	7.80	6.83 ± 1.09	5.20	9.40	6.90 ± 1.52	4.00	9.20	7.21 ± 1.90
Hct (%)	37.20	49.50	46.13 ± 5.01	38.80	49.00	43.53 ± 4.24	38.00	48.00	43.53 ± 3.46
Plt ($\times 10^{9}$/l)	198.0	386.0	266.6 ± 61.9	197.0	366.0	293.2 ± 66.3	238.0	334.0	283.3 ± 33.8
Cholesterol (mmol/l)	3.63	6.94	4.61 ± 1.15	3.75	5.20	4.58 ± 0.66	3.58	5.71	5.00 ± 0.81
LDL (mmol/l)	0.9	4.03	2.53 ± 1.07	1.12	2.40	1.95 ± 0.49	1.40	3.35	2.72 ± 0.78
HDL (mmol/l)	1.07	1.67	1.32 ± 0.2	1.12	5.67	2.12 ± 1.75	1.13	2.11	1.65 ± 0.42
TG (mmol/l)	0.62	1.98	1.33 ± 0.5	0.84	1.65	1.43 ± 0.31	0.56	0.88	0.68 ± 0.15
% HDL (%)	17.4	53.2	31.9 ± 11.7	28.5	53.2	34.9 ± 9.4	29.0	37.1	34.2 ± 3.2
ALT (U/l)	21.0	35.0	26.3 ± 4.9	14.0	39.0	29.2 ± 9.5	12.0	43.0	29.3 ± 11.7
AST (U/l)	20.0	32.0	23.6 ± 4.0	12.0	32.0	25.8 ± 8.1	13.0	33.0	23.0 ± 7.7
Creatinine (µmol/l)	54.1	93.4	76.4 ± 11.9	63.7	105.0	81.2 ± 16.0	57.8	112.0	85.3 ± 18.5
Urea (mmol/l)	3.74	6.97	5.29 ± 1.19	3.24	6.10	4.85 ± 1.22	2.36	4.05	3.37 ± 0.66
Na^+ (mmol/l)	138.0	143.0	141.0 ± 1.73	137.0	145.0	141.2 ± 3.5	136.0	145.0	140.2 ± 3.9
K^+ (mmol/l)	3.39	5.67	4.41 ± 0.72	3.79	4.7	4.2 ± 0.37	3.80	4.35	4.08 ± 0.18
Glucose (mmol/l)	4.83	6.1	5.57 ± 0.52	4.23	6.1	5.46 ± 0.73	4.93	5.90	5.38 ± 0.33

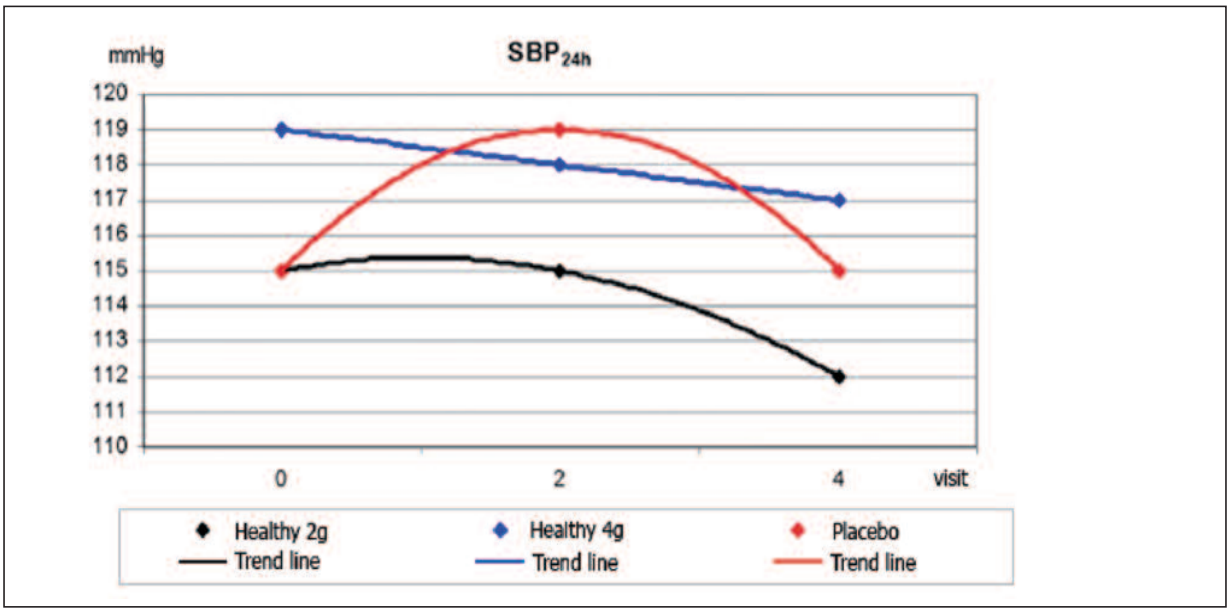

Figure 1. Graphical representation of average SBP values in studied groups for 24-hour measurement.

supplemented with 2 g of L-arginine (the decrease was statistically significant; $p<0.05$; Figure 5, Table III). No statistically significant differences were found among studied groups concerning initial and end values of DBP measured during night (Figure 6, Table IV) and between initial and end values of mean blood pressure (MAP) measured 24-hour for all subgroups (Figure 7, Table V).

Discussion

Several studies suggest that supplementation with L-arginine may be beneficial in the treatment of patients with arterial hypertension due to its influence on nitric oxide (NO) synthesis and function of endothelium[16]. While the decrease of NO bioavailability is the key dysfunction of endotheli-

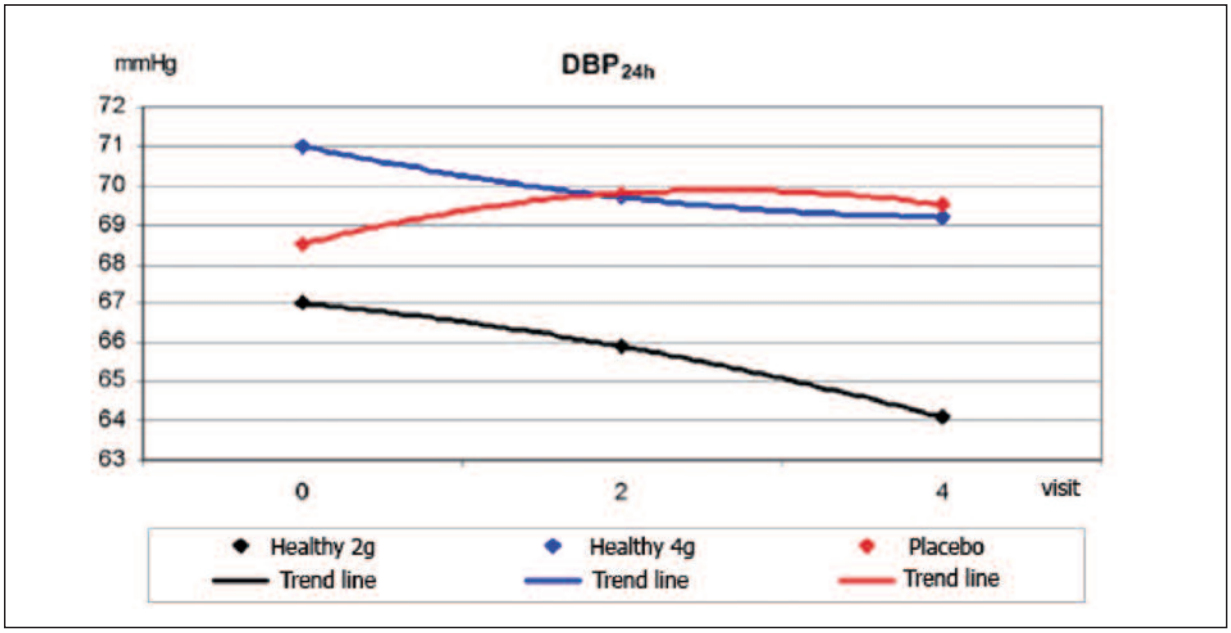

Figure 2. Graphical representation of average DBP values in studied groups for 24-hour measurement.

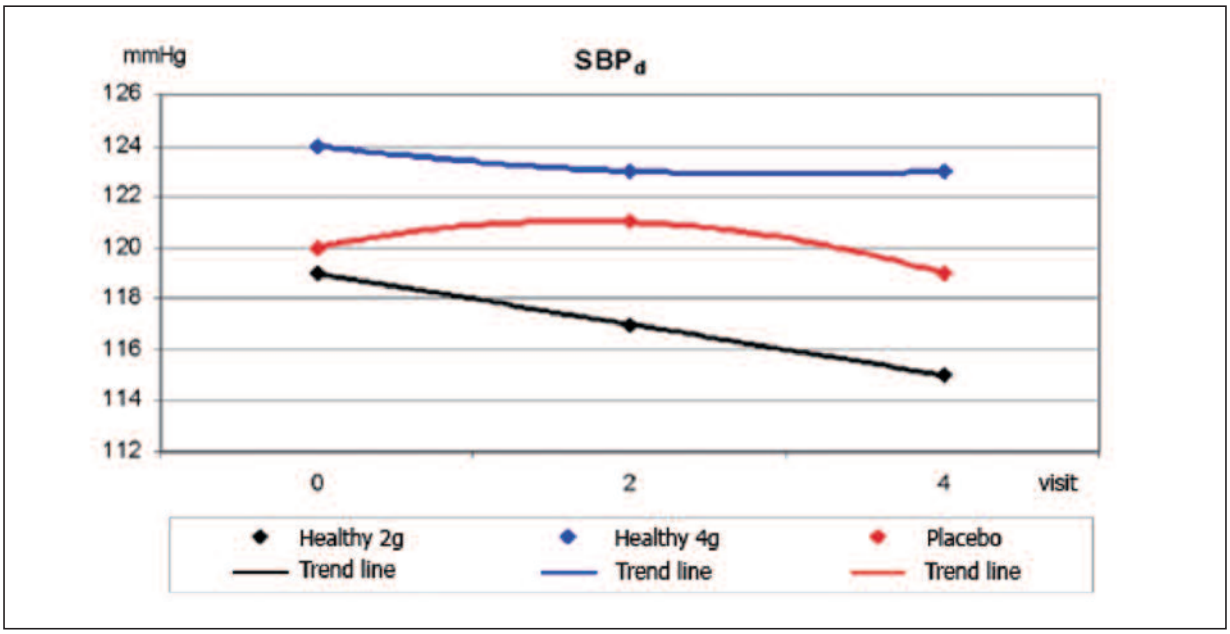

Figure 3. Graphical representation of average SBP values in studied groups for day measurement.

um in hypertension, delivering the substrate for its synthesis is considered a rational approach. One of the first studies that associates the improvement of NO bioavailability with supplementation with L-arginine was the research conducted on the progeny of patients suffering arterial hypertension which showed that L-arginine normalized function of endothelium[17]. In patients with mild and moderate hypertension an oral supplementation with L-arginine (3 × 2 g per 24-hour) decreased blood pressure and improved the function of endothelium after 1 week of treatment[18]. Intravenous infusion of L-arginine (500 mg/kg during 30 min) decreased the mean blood pressure by 8% and plasma levels of endothelin 1 and angiotensin II in patients with mild hypertension[19-21]. 6-month supple-

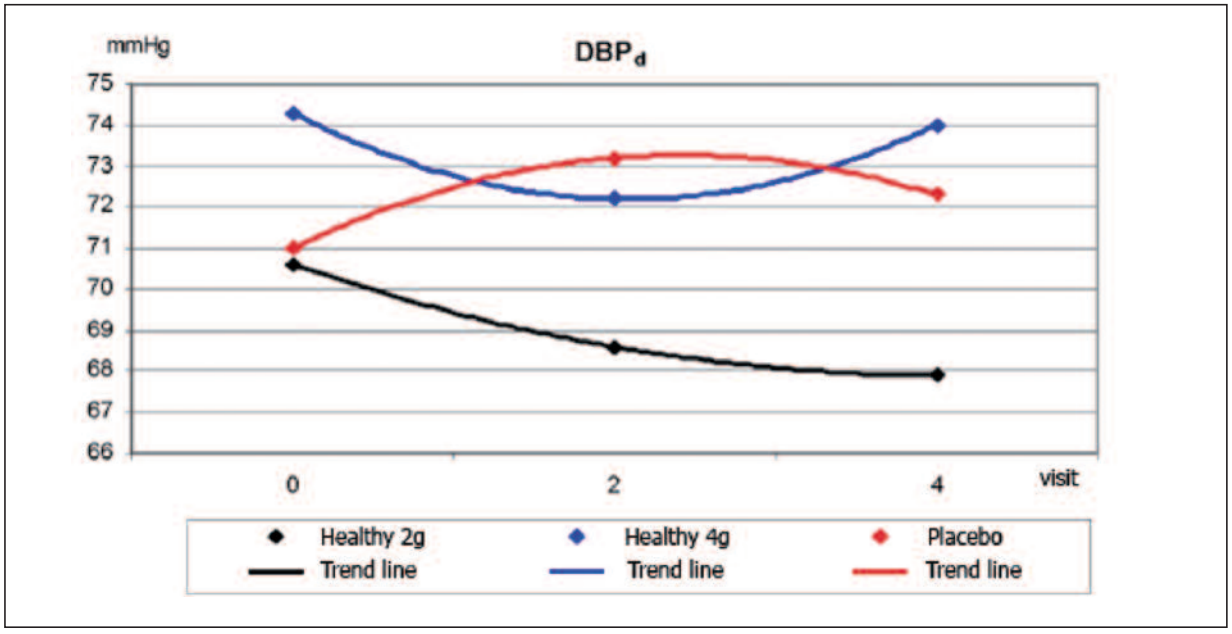

Figure 4. Graphical representation of average DBP values in studied groups for day measurement.

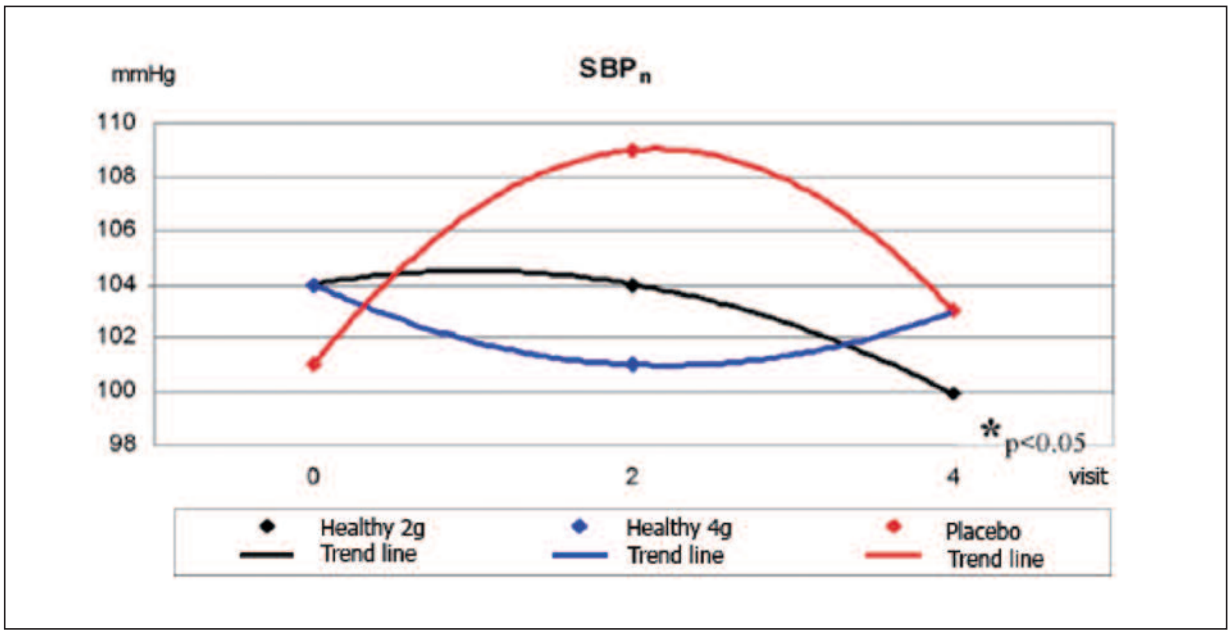

Figure 5. Graphical representation of average SBP values in studied groups for night measurement.

mentation with L-arginine considerably decreased total peripheral resistance in patients with multiple cardiovascular risk[3]. Hemodynamic results of L-arginine was also observed in healthy people. A dose-dependent decrease of blood pressure has been shown in healthy people[22-24]. In adult people with correct blood pressure a 30-minute enema of L-arginine (500 mg/kg) led to decrease of average blood pressure by 9% which was associated with the increase of endogenic NO synthesis[25]. Observed effect took place also in normotensive children who showed fast decrease of average blood pressure after application of L-arginine (500 mg/kg during 30 min)[26].

In studies conducted so far the hypotensive effect of supplementation with L-arginine was esti-

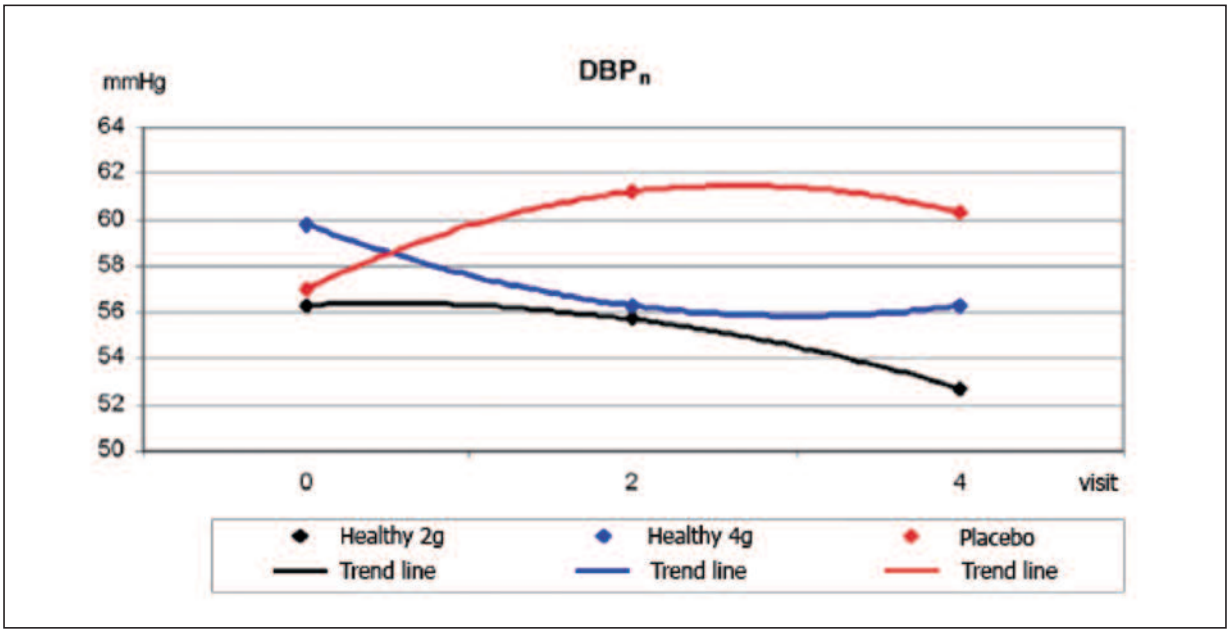

Figure 6. Graphical representation of average DBP values in studied groups for night measurement.

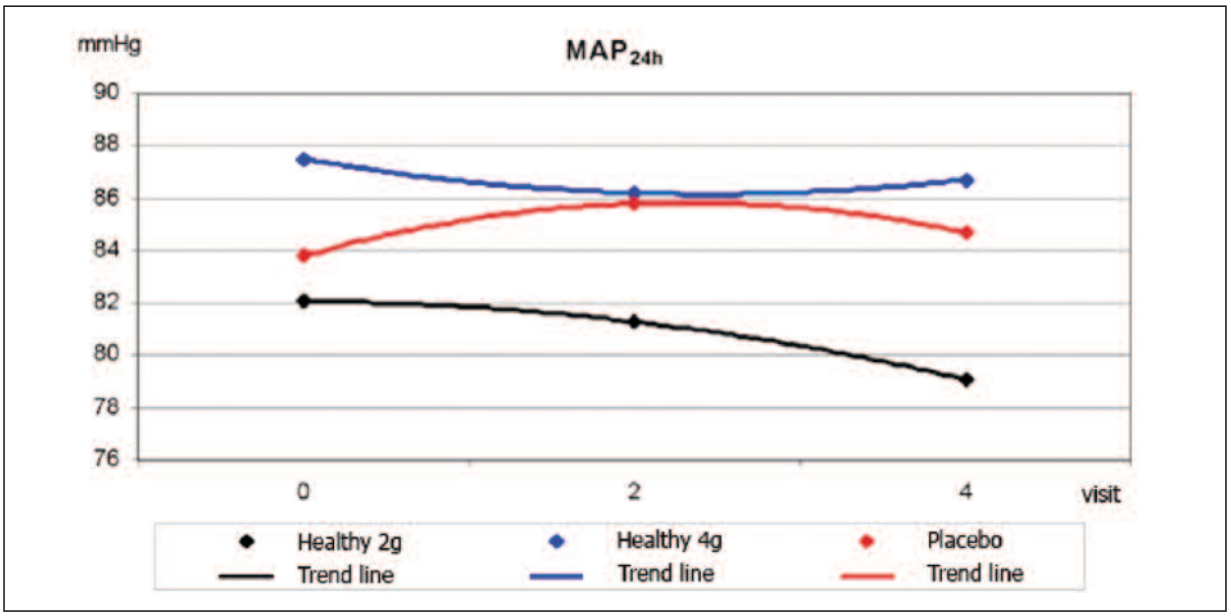

Figure 7. Graphical representation of average MAP values in studied groups for 24-hour measurement.

mated in healthy people using only traditional measurements of blood pressure – no research was conducted using ABPM. The results are inconsistent[24,27,28]. Therefore, we decided to conduct a randomized, placebo-controlled clinical investigation on the group of healthy people. It is worth noticing that this study is (according to the literature) the first research estimating hypotensive effect of L-arginine in healthy people using ABPM.

Oral form of L-arginine supplementation was chosen because of longer half-time compared to intravenous application[29]. Oral supplementation is preferred in long-term treatment and applied doses allowed the increase of consumption of L-arginine by 200% compared to average diet (5.4 g of L-arginine)[30].

No adverse reactions were observed during the whole period of study which proves good safety profile of this amino acid, known from the literature[31].

As it was emphasized earlier, the present work is the first clinical trial of L-arginine in healthy people using ABPM – also as a method of qualification individuals for the research. It allowed us to exclude patients who, after verification by ABPM, would be qualified for hypotensive treatment in normal practice.

In all healthy subjects supplemented with L-arginine only a declining tendency was observed for 7 described ABPM parameters. However, clearly significant decreases of average systolic blood pressure was observed only in the group treated with lower dose of L-arginine (3 × 2 g per 24-hour). Hypotensive effect of L-arginine was primarily on parameters measured during night which may indicate a link between its activity and daily rhythm (parasympathetic nervous system).

In other comparisons, observed decreases in blood pressure did not reach statistical significance. Undoubtedly the decrease of blood pressure would be greater in traditional measurements. In ABPM lower values of blood pressure are observed due to technical issues resulting in some "flattening" of hypotensive response. In addition, there is no placebo effect, or is minimal in the case of evaluation in ABPM.

Considering obtained results, L-arginine has a non-significant hypotensive effect in healthy people. It cannot be excluded that L-arginine does not improve function of endothelium in healthy people.

Conclusion

In healthy people oral 4-week supplementation with L-arginine (6 or 12 g per 24-hours) leads to nonsignificant decrease of systolic and diastolic blood pressure measured with ABPM; observed decrease was greater during night.

Table III. Characteristics of systolic blood pressure for 24-hour, day and night measurement.

SBP	Group	Visit 0			Visit 2			Visit 4			Visit 5		
		Min	Max	M ± SD	Min	Max	M ± SD	Min	Max	M ± SD	Min	Max	M ± SD
24 h	I	106	121	115 ± 6.0	105	122	115 ± 6.7	104	117	112 ± 5.2	103	118	111 ± 5.8
	II	106	124	119 ± 6.9	105	123	118 ± 7.2	104	123	117 ± 7.1	105	125	119 ± 8.5
	III	105	120	115 ± 7.0	105	127	119 ± 9.9	104	123	115 ± 8.9	102	124	116 ± 10.1
Day	I	107	125	119 ± 7.4	108	123	117 ± 6.1	107	122	115 ± 5.3	105	120	114 ± 6.1
	II	105	131	124 ± 9.0	108	130	123 ± 8.9	110	129	123 ± 7.4	108	129	123 ± 9.1
	III	105	127	120 ± 9.5	108	130	121 ± 10.0	107	127	119 ± 9.3	104	128	118 ± 11.5
Night	I	98	113	104 ± 4.8	91	117	104 ± 9.2	94	107	99.9 ± 5.8	90	107	100 ± 6.3
	II	97	118	104 ± 7.9	91	108	101 ± 5.9	94	110	103 ± 5.7	95	111	103 ± 6.2
	III	98	103	101 ± 1.8	95	114	109 ± 7.6	94	108	103 ± 5.8	89	112	105 ± 9.1

Table IV. Characteristics of diastolic blood pressure for 24-hour, day and night measurement.

DBP	Group	Visit 0			Visit 2			Visit 4			Visit 5		
		Min	Max	M ± SD	Min	Max	M ± SD	Min	Max	M ± SD	Min	Max	M ± SD
24 h	I	62	72	67 ± 3.0	61	73	65.9 ± 4.3	58	74	64.1 ± 5.8	57	72	62.4 ± 4.5
	II	62	79	71 ± 6.1	60	76	69.7 ± 5.4	62	75	69.2 ± 4.4	59	75	69.8 ± 6.5
	III	60	60	68.5 ± 5.5	61	78	69.8 ± 7.6	61	77	69.5 ± 8.3	58	74	68.0 ± 8.8
Day	I	64	74	70.6 ± 3.1	65	75	68.6 ± 3.5	62	80	67.9 ± 3.8	60	71	65.9 ± 6.5
	II	64	82	74.3 ± 6.2	65	80	72.2 ± 5.1	70	80	74.0 ± 3.7	62	82	72.3 ± 6.5
	III	61	75	71.0 ± 5.5	63	82	73.2 ± 8.47	63	82	72.3 ± 9.5	60	78	70.3 ± 8.7
Night	I	52	62	56.3 ± 4.0	49	65	55.7 ± 5.7	45	61	52.7 ± 6.7	47	61	55.0 ± 5.1
	II	52	68	59.8 ± 6.9	49	63	56.3 ± 5.3	48	65	56.3 ± 5.3	47	67	56.7 ± 6.0
	III	52	60	57.0 ± 3.1	53	67	61.2 ± 6.5	52	66	60.3 ± 6.5	49	67	60.8 ± 7.5

Table V. Characteristics of average blood pressure in 24-hour measurement for studied groups during 0, 2, 4, and 5 visit.

MAP	Group	Visit 0			Visit 2			Visit 4			Visit 5		
		Min	Max	M ± SD	Min	Max	M ± SD	Min	Max	M ± SD	Min	Max	M ± SD
24 h	I	77	85	82.1 ± 2.9	76	86	81.3 ± 3.95	75	84	79.1 ± 4.1	72	85	78.7 ± 4.7
	II	77	95	87.5 ± 5.9	76	93	86.2 ± 5.7	77	93	86.7 ± 5.7	73	99	86.7 ± 8.8
	III	75	88	83.8 ± 7.3	76	93	85.8 ± 7.3	75	93	84.7 ± 9.2	72	92	84.3 ± 9.0

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