Endothelial dysfunction in adolescents with arterial hypertension: results of rheovasographic evaluation and heart rate variability analysis

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Summary

Background As a major regulator of local vascular homeostasis, the endothelium maintains vascular tone through the balance between vasodilatation and vasoconstriction. Upsetting this tight balance leads to endothelial dysfunction . The latter is thought to be a marker of future cardiovascular events in hypertensive patients.
The purpose of this research was to assess endothelial vasomotor function with relation to heart rate variability in adolescents with arterial hypertension.

Material and methods 56 adolescents (33 males, 23 females, aged 22 ± 2 years) were subdivided into equal groups (regarding gender, age, body mass index and genetic burden) according to hypertension appearance and smoking habits. All of them underwent forearm rheovasography with measurements of reactive hyperemia test heart rate variability being taken (a five-minute recording). As reliable values for evaluating endothelial function, relative changes in the peak blood flow velocity (ΔdZ/dT) and pulse blood volume (ΔdV) at the 1st min after reperfusion were used. The following parameters of the time (RRNN, SDNN, RMSSD, pNN50, CV) and frequency (TP, VLF, LF, HF; LF/HF) domain analysis were used for assessing heart rate modulation.

Results Our analysis elicited a significant difference in both velocity and volume characteristics between hypertensive smokers and healthy individuals. Endothelial function in hypertensive non-smoking patients and normotensive smokers was also impaired. Heart rate variability was decreased and sympathetic tone prevailed in hypertensive adolescents. Both are associated with endothelial dysfunction.

Conclusions Endothelial function is likely to be impaired in hypertensive adolescents, particularly among those who smoke. Moreover, heart rate variability is decreased and sympathetic tone prevails with relation to endothelial dysfunction towards the autonomic imbalance.

key words: arterial hypertension, adolescents, endothelial dysfunction, rheovasography, heart rate variability, vegetative tone

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Introduction

Arterial hypertension is an increasingly important medical and public health issue. Although it is most often considered a disease of old age, it is prone to appear in adolescents in increasing frequencies [1], despite important advances in our understanding of its pathophysiology and the availability of effective treatment strategies. Moreover, the precursors are often present in adolescents long before the clinical-

ly-accepted definitions of hypertension in adults are manifested [2].

Endothelial dysfunction is thought to be a marker of future cardiovascular events in hypertensive patients [3] since the endothelium is a major regulator of local vascular homeostasis through synthesis and releasing various factors that modulate angiogenesis, hemostasis, permeability, as well as vascular tone.

Due to harmful substances in tobacco smoke which produce oxidative stress, both acute and passive smoking is one of the most important aggressors of endothelial function [4–13]. On the other hand, increased sympathetic activation has been demonstrated to also contribute to the impairment of endothelial function [14, 15].

Aims and objectives

The objectives of the study were to evaluate endothelial function (flow-mediated endothelium-dependent vasodilation) via bioimpedance technology in adolescents with arterial hypertension, as well as to reveal associations between endothelial dysfunction and disturbances in cardiovascular vegetative regulation.

Material and methods

We studied 56 persons (see tab. I) in whom no differences were found regarding age, gender, body mass index and genetic burden. Patients suffering from arterial hypertension (mild to moderate) appeared not to have been treated previously. Those with blood pressure elevation due to secondary causes, or those with concomitant pathologies, were excluded.

The study protocol was approved by the Ethics Committee of Grodno State Medical University. Written informed consent for participation in the study was given by all subjects.

All of these subjects underwent forearm rheovasography (the bioimpedance method) with a reactive hyperemia test via the hard- software system known as "IMPECARD"[6, 16]. Reactive hyperemia was produced with 50 mmHg extra being pumped into the blood pressure cuff in order to cause an occlusion of the brachial artery. Patients were administered orthophene in a dose of 25 mg, 30–40 minutes before the examination to block prostacyclin-mediated vasodilation, although it appears to have a more limited role in the maintenance of vasodilator tone in human beings than previously thought. The relative changes of peak blood flow velocity (DdZ/dT) and pulse blood volume (DdV) captured at the first minute following reperfusion, were considered as informative parameters which highly correlate with flow-mediated vasodilations measured sonographically. As well as the dynamics of the values were assessed at the 3rd and 5th minutes.

Vegetative tone was assessed in compliance with heart rate variability values [17–23] (time and frequency domain analysis, short-term recording) via hard- and software system known as "BRIZ M". The following parameters were analyzed: all normal RR intervals (RRNN), the standard deviation of all normal RR intervals (SDNN), the square root of the mean of the squared differences between adjacent normal RR-intervals (RMSSD), the percentage of differences between adjacent normal RR-intervals that are > 50 ms (pNN50), the variability coefficient (CV), the total power of the spectrum (TP), high frequency (HF), low frequency (LF), very low frequency (VLF) components, as well as their relative (HF%, LF%, VLF%) and normalized values (HFnorm, LFnorm), LF/HF ratio.

All studies were performed in the morning, after overnight fasting, in a quiet room with a constant temperature (20–22°C) after a period of adaptation to the environmental conditions of 10–15 minutes. The subjects remained supine throughout the study. The patients were requested to breath quietly, not to move or cough. Smokers were asked not to smoke before the examination

The statistics tools used include descriptive ones (all data is expressed as Mean; ± 95% confidence interval), the Mann-Whitney U test, Yates' corrected

Table I. Characteristics of groups

Group	n	Gender (M/F)	Age	Body mass index	Burdened heredity	Inclusion criteria	Exclusion criteria
1	20	6/14	22.3 ± 2.7	22.7 ± 1.3	6	Healthy individuals	Age > 30 years
2	15	11/4	21.1 ± 1.3	24.5 ± 2.1	7	Nonsmoking hypertensive adolescents	Secondary blood pressure elevation
3	13	8/5	22.2 ± 1.8	22.5 ± 1.7	3	Normotensive smoking persons	Concomitant internal diseases
4	8	6/2	23.6 ± 2.1	23.8 ± 3.2	4	Smoking patients with arterial hypertension	Previous prolonged treatment

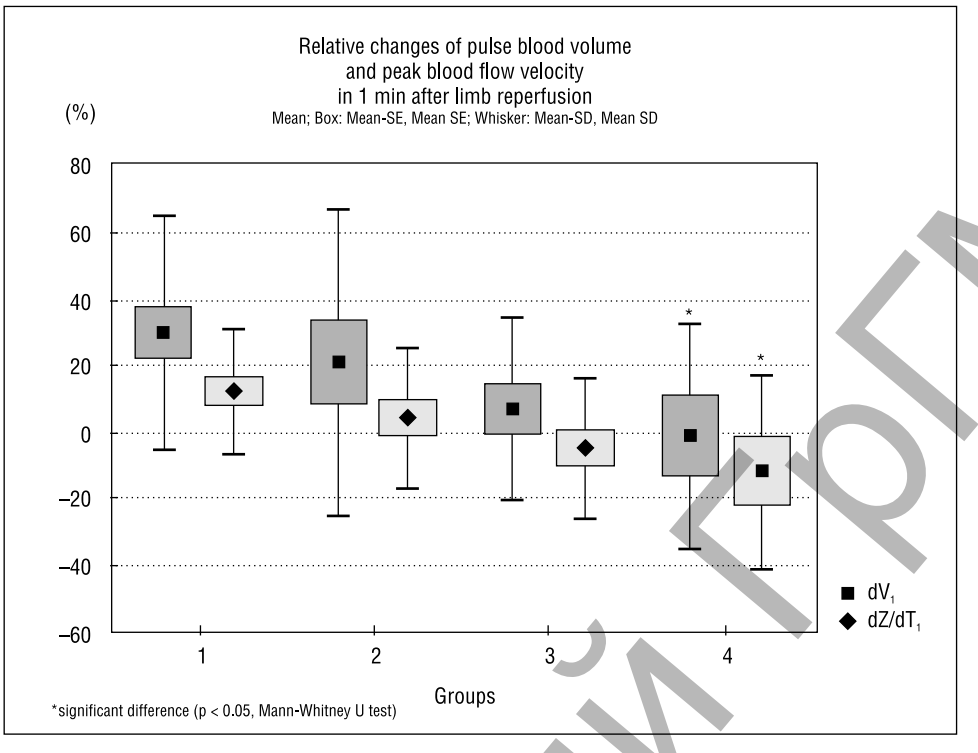

Figure 1. Rheovasographic values at 1 minute after reperfusion

Table II. Dynamics of rheovasographic values

Parameters	Time, min.	Group 1 Mean	Group 1 –95% CI	Group 1 +95% CI	Group 2 Mean	Group 2 –95% CI	Group 2 +95% CI	Group 3 Mean	Group 3 –95% CI	Group 3 +95% CI	Group 4 Mean	Group 4 –95% CI	Group 4 +95% CI
ΔdV (%)	1	**29.9**	13.4	46.4	**21.0**	–7.0	49.0	**7.0**	–9.7	23.6	**–1.0**	–29.3	27.3
	3	**18.7**	4.7	32.7	**13.9**	1.8	26.0	**–0.5**	–11.3	10.2	**17.8**	–8.6	44.3
	5	**16.0**	3.7	28.2	**6.9**	–8.0	21.9	**10.3**	–5.6	26.1	**6.3**	–14.3	26.9
ΔdZ/dT (%)	1	**12.4**	3.7	21.2	**4.5**	–7.2	16.3	**–4.5**	–17.4	8.5	**–11.6**	–36.3	13.1
	3	**2.6**	–3.6	8.9	**7.9**	1.0	14.8	**–1.0**	–11.9	9.9	**4.3**	–12.6	21.3
	5	**1.7**	–4.6	7.9	**3.6**	–3.9	11.0	**–3.6**	–11.7	4.6	**–4.3**	–14.2	5.6

chi-square and Spearman's rank correlation co-efficient (Statistica 7.0 for Windows, Statsoft Inc.). Values of $p < 0.05$ were considered statistically significant.

Results

Following results were obtained (See fig. 1, 2 and tab. II–V).

Significant correlations were found in the group of hypertensive non-smoking adolescents for ΔdZ/ /dT1 and: RMSSD (R = 0.82), SDNN (R = 0.3), pNN50 (R = 0.38), %HF (R = 0.74), %LF (R = –0.51), LF/HF (R = –0.44) (See figs. 3–8).

Discussion

The statistical results brought out a statistically significant difference in the rheovasographic parameters between healthy individuals and smoking adolescents with arterial hypertension, whereas the changes observed in other groups did not achieve a level of statistical significance although values were lower then in controls. This resulted from the statistical bias of small groups and the wide range of values inside these groups. Obviously, an association of several factors is quite more harmful in comparison with those which are isolated. Thus, our data confirm the results of J.A. Panza *et al.* [4] and F. Pericone *et al.* [3] who studied interactions with essential hypertension, and A.M. Zeiher [13] and J. Stoner J. *et al.* [24]

Table III. Criteria of endothelial dysfunction degree

Endothelial dysfunction degree	Criteria
Normal	$\Delta dZ/dT_1 > 12\%$
Mild	$-2\% < \Delta dZ/dT_1 \leq 12\%$
Moderate	$-15\% < \Delta dZ/dT_1 \leq -2\%$
Severe	$\Delta dZ/dT_1 \leq -15\%$

who evaluated the effects of smoking on the endothelium. Moreover, we show that impedance technology is rather suitable for endothelial function assessment.

Endothelial reactivity worsened from group 1 to group 4 with the most frequent favorable "1a" variant occurring in the 1st group and the poorest "3c" in the 4th. Though the Brachial Artery Reactivity Task Force recommended 2-minutes of recording after cuff deflation during the reactive hyperemia test [25],

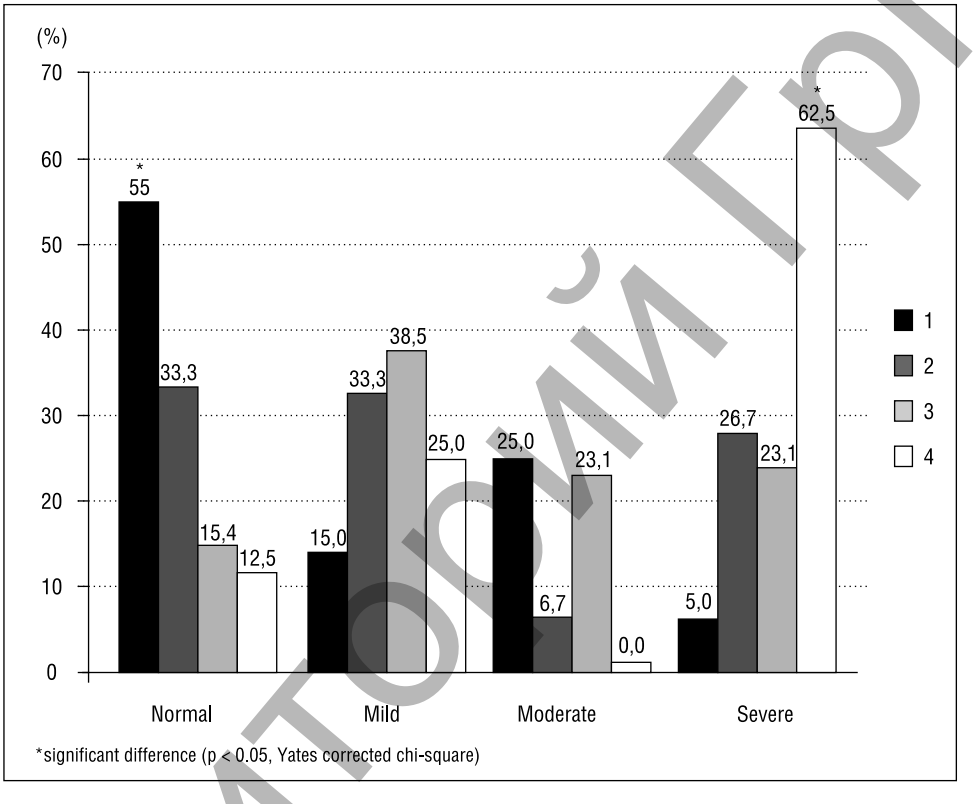

Figure 2. Distribution in groups with respect to endothelial dysfunction degree

Table IV. Endothelial reactivity patterns

Endothelial Reactivity	Pattern*	Group 1	Group 2	Group 3	Group 4
1 (positive)	a	11 (55.0%)**	6 (40.0%)	3 (23.1%)	1 (12.5%)
	b	0 (0.0%)	1 (6.7%)	2 (15.4%)	0 (0.0%)
	c	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2 (inertial, zero)	a	2 (10.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
	b	1 (5.0%)	2 (13.3%)	0 (0.0%)	0 (0.0%)
	c	2 (10.0%)	1 (6.7%)	2 (15.4%)	1 (12.5%)
3 (paradoxic, negative)	a	1 (5.0%)	4 (26.7%)	0 (0.0%)	2 (25.0%)
	b	1 (5.0%)	0 (0.0%)	3 (23.1%)	0 (0.0%)
	c	2 (10.0%)	1 (6.7%)	3 (23.1%)	3 (37.5%)**

*1a — positive reaction with peak at the 1st minute; 1b — positive reaction with peak at the 3rd minute; 1c — positive reaction with peak at the 5th minute; 2a — lack of reaction at the 1st minute, positive at the 3rd minute; 2b — lack of reaction at the 1st and 3rd minutes, positive at the 5th minute; 2c — lack of reaction within 5 minutes; 3a — negative reaction at the 1st minute, then positive at the 3rd minute; 3b — negative reaction within 3 minutes; 3c — negative reaction within 5 minutes
**significant difference ($p < 0.05$, Yates corrected chi-square)

Table V. Heart rate variability values in the groups

Parameters	Group 1			Group 2			Group 3			Group 4		
	Mean	–95% CI	+95% CI	Mean	–95% CI	+95% CI	Mean	–95% CI	+95% CI	Mean	–95% CI	+95% CI
RRNN [ms]	933	754	1112	894	754	1035	899	753	1044	912	741	1083
SDNN [ms]	73.9	45.3	102.4	64.4	42.1	86.8	69.8	44.4	95.2	66.0	31.6	100.4
RMSSD [ms]	74.9	42.5	107.2	51.4	24.5	78.4	65.2	33.1	97.3	45.6	8.6	82.6
pNN50 [ms]	40.1	17.3	62.8	28.5	10.6	46.3	32.8	9.1	56.4	22.4	–2.4	47.2
CV (%)	8.1	4.6	11.6	7.1	5.0	9.2	7.9	4.4	11.4	7.1	3.8	10.4
TP [ms^2]	6521	1581	11 460	5024	2129	7919	5609	1504	9714	5130	819	9441
VLF [ms^2]	1954	114	3795	2373	941	3806	2180	–325	4685	2568	–423	5559
LF [ms^2]	1937	70	3805	1241	713	1770	1698	326	3071	1254	–210	2718
HF [ms^2]	2629	691	4567	1410	88	2731	1555	–166	3276	1308	–911	3527
VLF (%)	31.3	18.4	44.2	48.8	38.1	59.4	35.4	19.0	51.7	54.8	18.4	91.3
LF (%)	26.7	15.9	37.4	29.5	21.1	37.8	28.7	19.7	37.6	24.6	2.8	46.3
HF (%)	42.0	24.8	59.3	21.8	11.1	32.5	36.0	15.8	56.3	20.6	0.1	41.1
LF norm, n.u.	40.4	23.8	57.0	59.9	43.0	76.7	46.8	23.7	69.9	56.9	40.2	73.5
HF norm, n.u.	59.6	43.0	76.2	40.1	23.3	57.0	53.2	30.1	76.3	43.1	26.5	59.8
LF/HF	0.9	0.2	1.5	2.6	0.7	4.4	1.2	–0.1	2.4	1.5	0.7	2.3

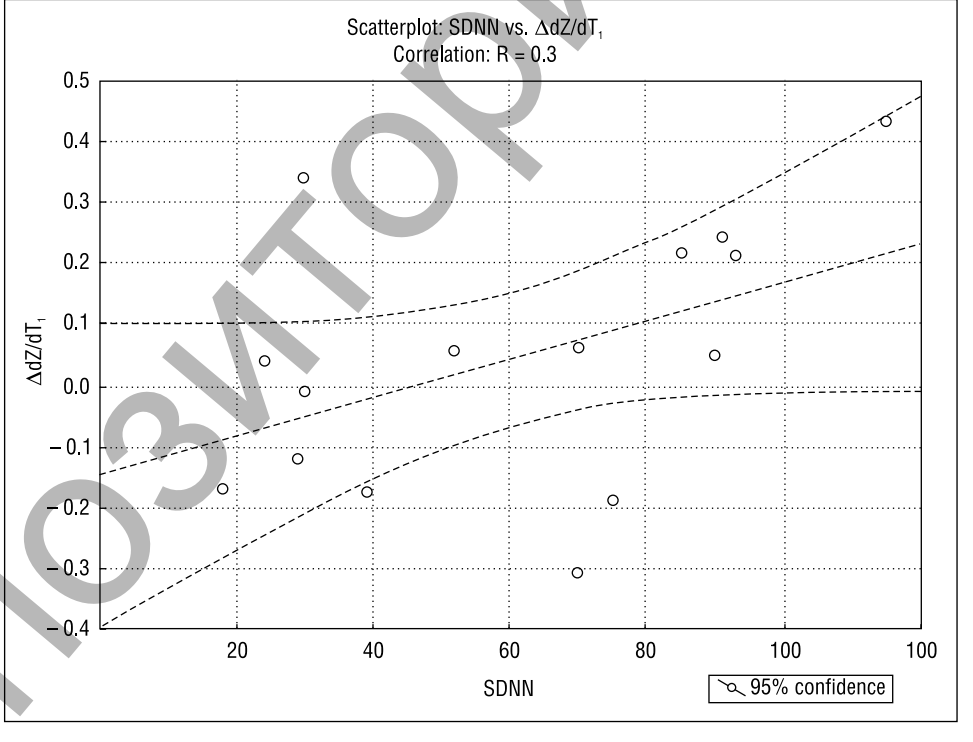

Figure 3. Relationship between relative change of peak blood flow velocity and standard deviation of all normal RR intervals

we suggested prolonging our analysis up to 5 minutes. We suppose that this determination of the reactivity patterns is rather informative and useful in endothelial vasomotor function testing, as it reflects the reserve scope of the endothelium for nitric oxide secretion with response to shear stress.

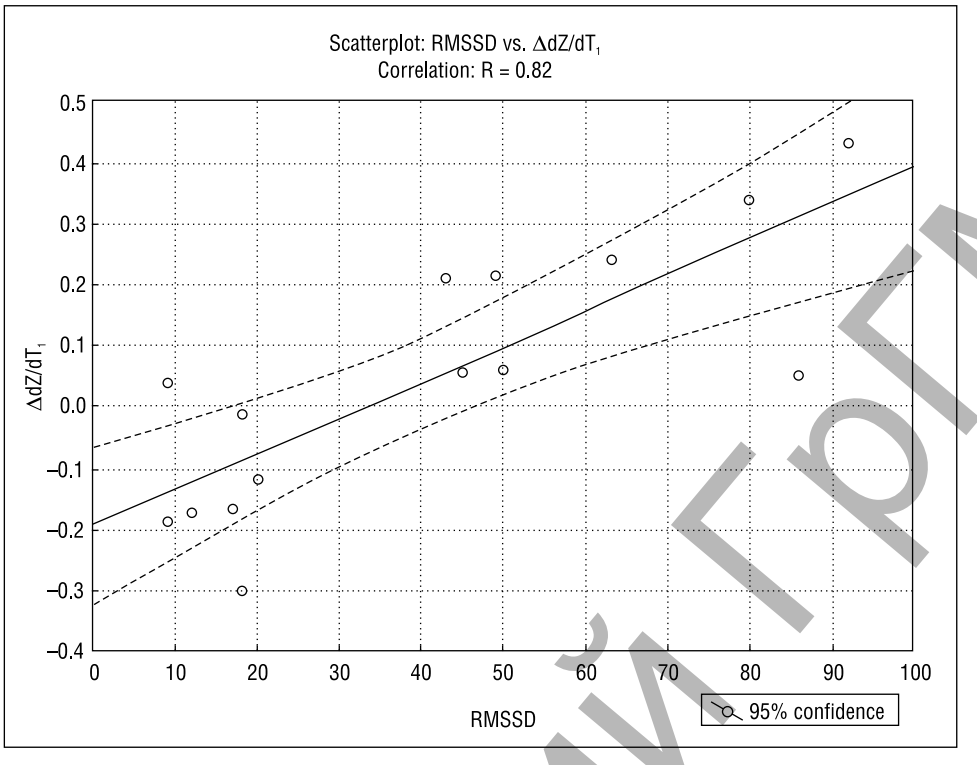

Figure 4. Relationship between relative change of peak blood flow velocity and square root of the mean of the squared differences between adjacent normal RR-intervals

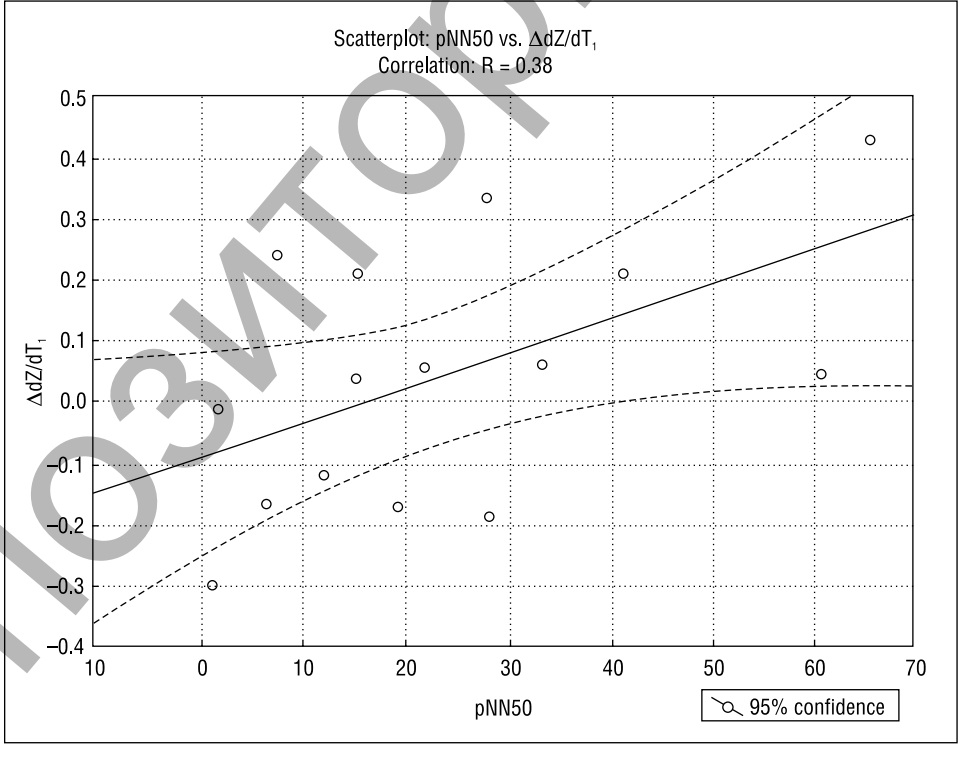

Figure 5. Relationship between relative change of peak blood flow velocity and percentage of differences between adjacent normal RR-intervals that are > 50 ms

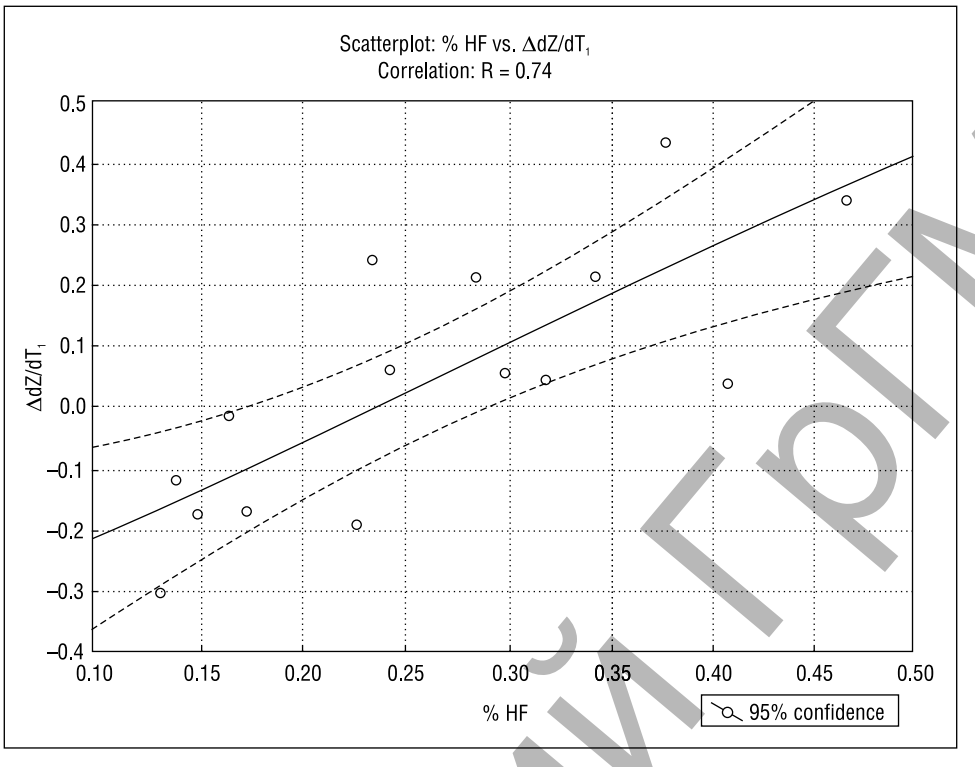

Figure 6. Relationship between relative change of peak blood flow velocity and high frequency percentage

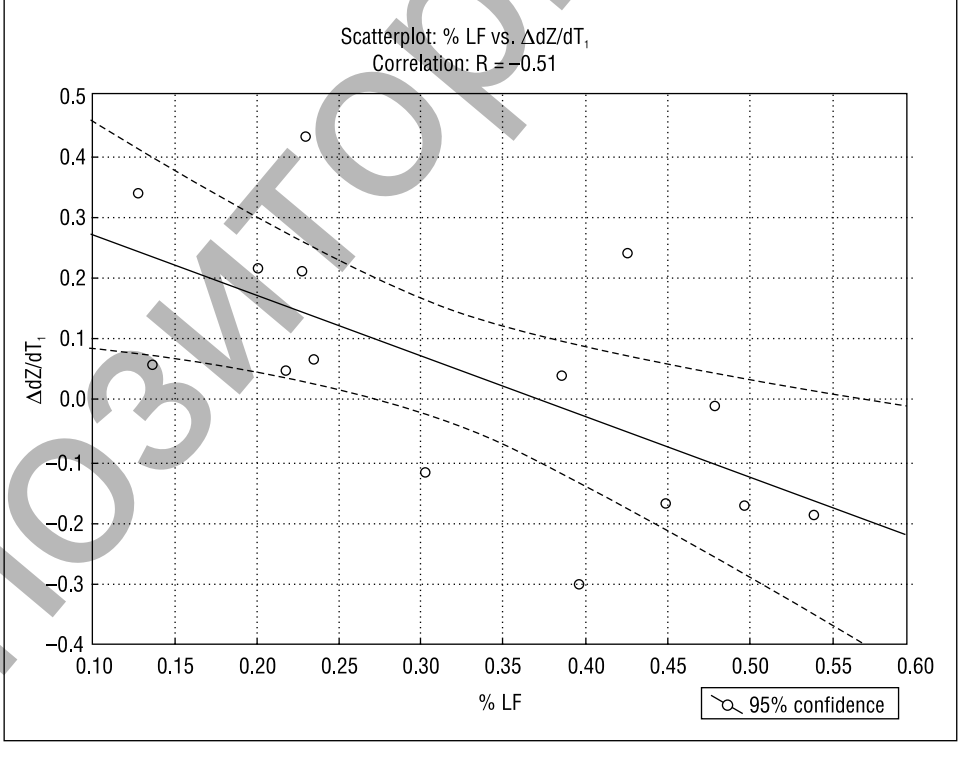

Figure 7. Relationship between relative change of peak blood flow velocity and low frequency percentage

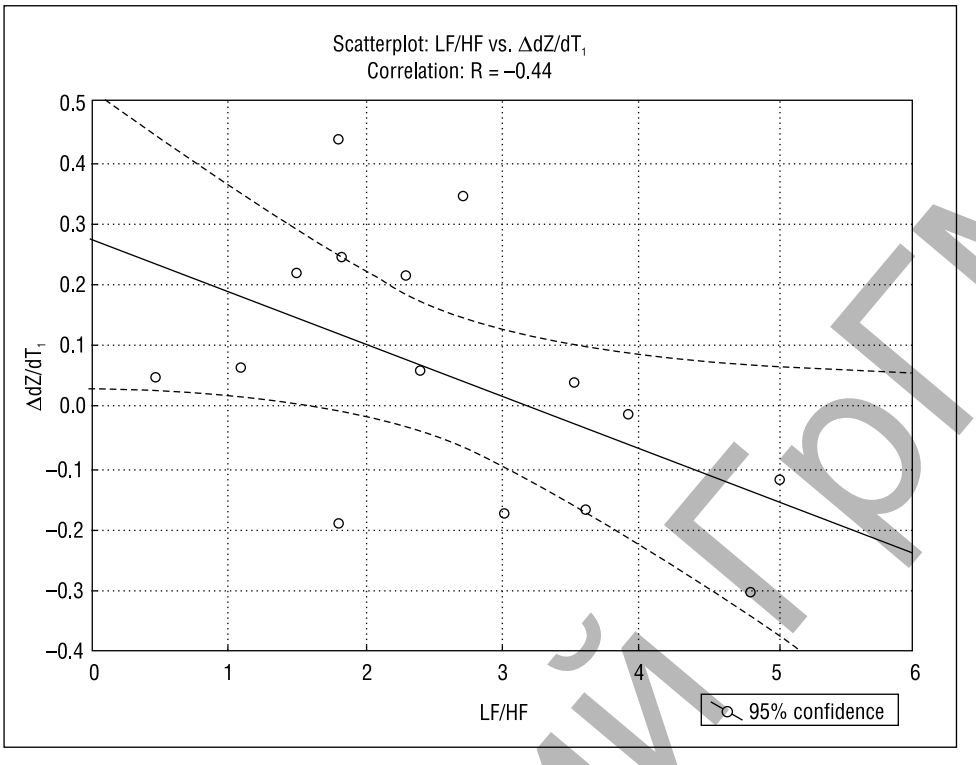

Figure 8. Relationship between relative change of peak blood flow velocity and low to high frequency ratio

Normal endothelial function i.e. sufficient increase in blood flow, was obtained significantly more often in healthy individuals, although endothelial dysfunction was found to be present in them too. It is possible that a variety of endogenous (such as hormonal baseline, etc.) and exogenous (such as mental stress, etc.) factors, that could not be considered in the present study, influence endothelial function. This once again indicates the systemic features of endothelial dysfunction as the endothelium is a receptor of a variety of stimuli. Severe dysfunction, i.e. paradoxical vasoconstriction in response to reactive hyperemia, was seen more often in hypertensive adolescents who smoked. On the other hand, normal function was restored in those patients who were hypertensive and smoked. Thus, these lesions are probably mild, benign and potentially reversible, as the hypertension was characterized with mild to moderate elevation of blood pressure, as well as there being no heavy smokers among the patients under observation.

Generally normal, but decreased, variability values and increased sympathetic tone in heart rate modulation were obtained in hypertensive adolescents and those who smoked. These data agree with those of D.F. Dietrich *et al.* [26] who has proved heart rate variability to be decreased in patients with passive exposure to tobacco smoke, and A. Stys *et al.* [23] regarding heart rate variability in patients suffering from arterial hypertension, among other clinical applications of this method. However, our values are practically similar in all four groups with a tendency to be impaired in the presence of both factors. Therefore, these differences were particularly insignificant. There was an association between the degree of endothelial dysfunction and decreased heart rate variability, as well as an autonomic imbalance towards sympathetic prevalence in patients with arterial hypertension, that at least, in part, coincides with the data of Y. Takei *et al.* [14].

Thus, the endothelium of hypertensive adolescents has a decreased ability to induce vascular relaxation because of one, or several, mechanisms: decreased synthesis, impaired response or increased inactivation of NO. Hypertension-associated endothelial dysfunction in adolescents has a strong possibility of being reversed by a pharmacological treatment with antihypertensive drugs. The latter may represent a new target for therapeutic intervention in essential hypertension. Moreover, the consideration of autonomic imbalance is likely to bring additional benefits.

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