

Effects of antihypertensive treatment on cardiovascular autonomic control: a prospective study

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ABSTRACT

Objective: The aim of study was to propose an approach to the control of dynamics of autonomic dysfunction in cardiovascular system (CVS) under antihypertensive treatment (AT) in patients with arterial hypertension (AH), based on individual features of synchronization of 0.1-Hz rhythms in heart rate (HR) and photoplethysmogram (PPG) and spectral indices of heart rate variability (HRV).

Methods: We designed prospective cohort diagnostic accuracy and studied 105 AH patients (66 females) aged 47±8 years during 8 weeks. The HRV spectral indices and the index S of synchronization between the 0.1-Hz rhythms in HR and PPG during a tilt test are compared in their ability to control the AT with angiotensin-converting enzyme inhibitors (ACE-Is) (fosinopril or enalapril) and β-blockers (atenolol or metoprolol). We apply Shapiro-Wilk, Mann-Whitney U and Wilcoxon tests.

Results: It is shown that the power of low-frequency (LF) band in HRV spectrum and index S can be used as criteria for initial assessment of the status of autonomic regulation in AH patients. The patients with S<25% in vertical body's position and LF>250 ms² in horizontal body's position require ACE-Is treatment. The AH patients with LF<350 ms² and S<30% in vertical body's position require β-blocker treatment. The AH patients with S>25% and LF>250 ms² in horizontal body's position do not require any ACE-Is or β-blocker treatment. Both drug groups can be used in patients with low values of index S and low power of LF band in HRV spectrum.

Conclusion: The control of AT can be carried out in AH patients taking into account the individual features of autonomic dysfunction in CVS. Sensitivity and specificity of our approach were 65% and 73%, respectively. (*Anadolu Kardiyol Derg* 2014; 14: 701-10)

Key words: arterial hypertension, autonomic dysfunction, 0.1-Hz rhythms, ACE inhibitors, β-blockers

Introduction

It is known that 0.1-Hz rhythms in the cardiovascular system (CVS) characterize the properties of its autonomic regulation (1-3). These rhythms are observed in heart rate (HR) (4-7), blood pressure (BP) (1, 2, 4, 5, 8) and photoplethysmogram (PPG) signals (1, 2, 9-12). It is evident that they have both the central (3, 9, 13, 14) and baroreflex (15, 16) origin. The 0.1-Hz rhythm in HR is an estimate of combined vagal and β-sympathetic activity (17), whereas the 0.1-Hz rhythm in peripheral BP is an estimate of α-sympathetic activity (18). It has been found that 0.1-Hz rhythms can be synchronized between themselves (10, 12, 19). From physiological viewpoint, the synchronization of 0.1-Hz rhythms is the result of adequate functional interaction of CVS parts. The quality of their synchronization is higher in healthy subjects than in patients with cardiovascular disease (12). In

previous studies we have shown the importance of assessment of synchronization between the 0.1-Hz rhythms in HR and PPG for selection of optimal dose of beta-blocker treatment (20) and evaluation of the personal five-year risk of cardiovascular events in myocardial infarction patients (21).

0.1-Hz oscillations in PPG may be associated directly with baroreflexor regulation of BP (22). At the same time, a number of papers assert that 0.1-Hz oscillations in blood microcirculation are not associated with autonomic regulation (23-26). Taking into account the broad capture of distal vascular bed by PPG device, we are justified in assuming that 0.1-Hz oscillations in PPG signal have an autonomic component characterizing the regulation of the BP at the level of digital arteries. However, we cannot unambiguously define the contribution of microcirculatory bed including arterioles with sympathetic innervation to 0.1-Hz oscillations in PPG. To avoid the terminological confusion

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we will use throughout the paper the term PPG speaking about 0.1-Hz oscillations recorded by PPG device. Thus, in distinction to our previous papers (12, 20, 21), in the present one we only name the signal as PPG and do not interpret the origin of the considered oscillations.

According to the European Society of Cardiology (ESC) guidelines on heart rate variability (HRV) (6), three main spectral components are distinguished in a spectrum calculated from short-term recordings, namely, the components in the high-frequency (HF) range, 0.15-0.4 Hz, low-frequency (LF) range, 0.04-0.15 Hz, and very low-frequency (VLF) range, 0.003-0.04 Hz. The physiological explanation of these bands is known (4-7).

Autonomic dysfunction has an important role in pathogenesis of arterial hypertension (AH) (27, 28). Baroreflex disturbance was presented often in hypertensive patients (28, 29). The baroreflex features advantage over HRV indices has been shown for prevention of ambulatory hypertension at early stage (30). The problem of using baroreflex BP regulation for correction of AH treatment has attracted much attention in recent years. Angiotensin-converting enzyme inhibitors (ACE-Is) and cardioselective β -blockers have different influence on the autonomic regulation of CVS. Cardioselective β -blockers influence the heart regulation primarily, whereas ACE-Is act at the level of vascular bed. Various aspects of influence of these antihypertensive drugs on baroreflex were studied (31, 32). Positive effect of ACE-Is on baroreflex, which was assessed by HRV indices, was shown (33). It seems promising to use synchronization of 0.1-Hz rhythms in CVS for assessing the effectiveness of treatment in AH patients.

Tilt test is used traditionally for diagnosis of syncope (34, 35) and orthostatic hypotension (36), study of sympathetic activity (37), study of the influence of various agents and factors on autonomic control (38), etc. Therefore, the use of tilt test for study of drug influence on autonomic regulation, including baroreflex, is appropriate.

The aim of this study was to propose a new approach to antihypertensive treatment in AH patients taking into account the individual features of autonomic dysfunction in CVS estimated by synchronization between the 0.1-Hz rhythms in HR and PPG as well as spectral indices of HRV. Detailed comparison of drugs efficacy (fosinopril vs enalapril, atenolol vs metoprolol; see Study protocol section) was not the aim of this study.

Methods

Study design

The general design of our prospective cohorts study on accuracy of new diagnostic method is shown in Figure 1. The study was approved by the Ethics Committee and informed consent was obtained from all participants.

Study population

Our study included 105 patients with AH [66 (63%) females and 39 (37%) males aged 47 ± 8 years].

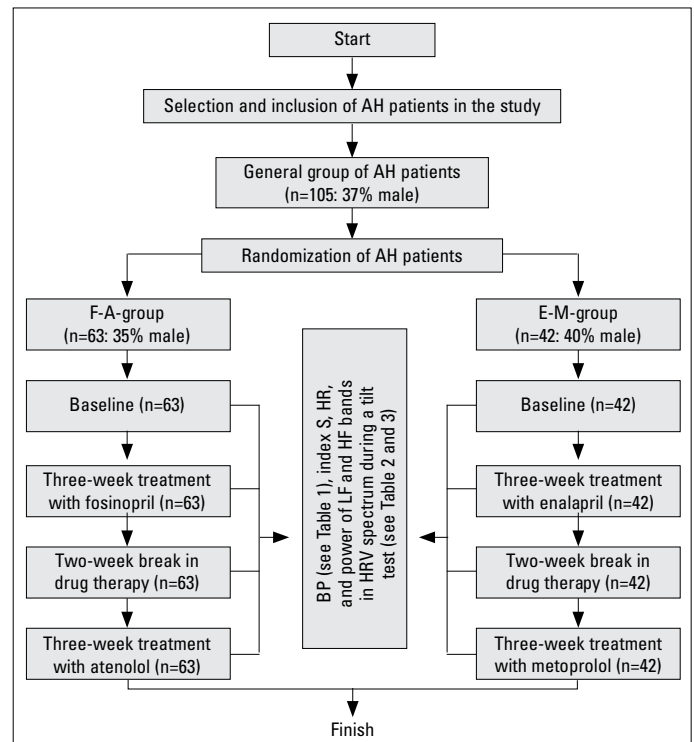


Figure 1. General design of the study

AH - arterial hypertension; E-M - enalapril and metoprolol; F-A - fosinopril and atenolol

We used the following criteria to enroll the patients in our study:

- i) the confirmed diagnosis of AH (39, 40),
- ii) age between 35 and 60 years,
- iii) hypertension of grade 1 or 2 (39, 40),
- iv) the absence of antihypertensive therapy within 7 days prior to the start of the study.

The patients were not included in our study if they matched the following criteria:

- i) subclinical organ damage in accordance with guidelines (41, 42),
- ii) established cardiovascular or renal disease in accordance with guidelines (41, 42),
- iii) diabetes mellitus,
- iv) valvular defect of the heart,
- v) abnormalities in HR impeding the analysis of HRV,
- vi) endocrine pathology,
- vii) chronic gastrointestinal diseases (hepatitis, gastric ulcer, duodenum disease and cholecystitis) chronic diseases of kidneys and other chronic diseases in the stage of exacerbation,
- viii) previous regular antihypertensive treatment with a satisfactory control of BP within 3 months prior to the start of the study.

Identification of exclusion criteria was performed during clinical examination, which included 12-lead electrocardiogram (ECG) in rest, laboratory investigations (hemoglobin, blood glucose, creatinine, lipids, etc.), Holter monitoring, exercise testing, carotid ultrasound, echocardiography (left ventricular ejection fraction, hypertrophy, valvular defect, etc.), microalbuminuria express test, kidney ultrasound, fundoscopy, etc.

Baseline variables and clinical examinations

All patients, enrolled in our study, had the confirmed diagnosis of 1-2 grades AH (two or more years before) and were prescribed antihypertensive drug treatment in prior primary care offices in accordance with 2007 ESC Guidelines (41). Our study started before the 2013 ESC Guidelines (42) were published.

Accepted inclusion and exclusion criteria suggest that the studied group of AH patients is characterized by the absence of influence of important organic damage factors on the autonomic regulation in CSV estimated by 0.1-Hz rhythms synchronization and HRV spectral indices. Previous antihypertensive therapy has no significant influence on autonomic regulation, because the patients were not treated within 7 days prior to the start of the study. Also the prior drug treatment was often not intensive and irregular, due to problems with patient compliance to routine ambulatory care.

Study protocol

The study has the following stages:

- i) first stage-three-week treatment with ACE-Is,
- ii) two-week wash-out period for ACE-Is treatment,
- iii) second stage - three-week treatment with cardio-selective β -blockers.

To examine autonomic control of CVS we carried out spectral analysis of HRV and estimated a degree of synchronization between the 0.1-Hz rhythms in HR and PPG. ECG, PPG measured on the middle finger of the subject's hand and respiration were simultaneously recorded during a tilt test. The tilt test protocol was the following:

- i) subject was lying in a horizontal position. It was a preliminary stage lasting 10 minutes without signal recording;
- ii) the signals were recorded within 10 minutes in the horizontal position of patient's body;
- iii) subject was put in a vertical position with a tilt angle of about 80°. To exclude the transients the signals were not registered within 5 minutes;
- iv) the signals were recorded within 10 minutes in the vertical position of patient's body.

The subjects were investigated in the afternoon fasting under spontaneous breathing. All signals were sampled at 250 Hz and digitized at 14 bits. The record of respiration was used to control evenness of breathing. We excluded from the analysis the series with forced inspiration and delays in breathing. For further analysis only ECG and PPG records without artifacts, extrasystoles and considerable trends were left.

Signals were recorded during the tilt test at the following checkpoints of our study:

- i) before starting treatment with ACE-Is,
- ii) after three-week treatment with ACE-Is,
- iii) after two-week break in drug therapy (i.e. two-week wash out period),
- iv) after three-week treatment with cardioselective β -blockers.

Two-week break in antihypertensive therapy was necessary to eliminate the influence of ACE-Is, used in the first stage of this study, on the autonomic regulation of CVS at the beginning of β -blocker therapy. During the wash-out period, all AH patients

were supervised by ambulatory physicians. In case of necessity, they were given emergency care around the clock.

In this study we used the following ACE-Is: fosinopril at the dose of 20 mg/day (one time per day at 8⁰⁰-8³⁰ a.m.) and enalapril at the dose of 20 mg/day (2 times per day with 10 mg at 8⁰⁰-8³⁰ a.m. and 8⁰⁰-8³⁰ p.m.) and the following β -blockers: atenolol at the dose of 100 mg/day (one time per day at 8⁰⁰-8³⁰ a.m.) and metoprolol tartrate at the dose of 100 mg/day (2 times per day with 50 mg at 8⁰⁰-8³⁰ a.m. and 8⁰⁰-8³⁰ p.m.).

All AH patients were assigned to two groups matched for clinical characteristics (Fig. 1). The first group was composed of patients (n=63; 65% females) treated sequentially with fosinopril and atenolol. We named this group as F-A-patients. The second group was composed of patients (n=42; 60% females) treated sequentially with enalapril and metoprolol. We named this group as E-M-patients. We had no preference in the choice of drugs for treatment. Anthropometric and clinical characteristics of both groups are presented in Table 1.

HRV and PPG

Spectral characteristics of HRV were calculated using parametric method of spectrum estimation based on autoregression model (order 14) construction. HF range (0.15-0.4 Hz) and LF range

Table 1. Anthropometric and clinical characteristics of F-A and E-M-patients

Parameter	F-A-patients (n=63)	E-M-patients (n=42)	P level
Age, years, Me (Q1, Q2)	46 (42, 52)	50 (41, 56)	0.060
Male sex, %	35%	40%	0.604
Height, cm, Me (Q1, Q2)	170 (164, 175)	170 (162, 172)	0.494
Weight, kg, Me (Q1, Q2)	80 (70, 89)	84 (75, 95)	0.262
BMI, kg/m ² , Me (Q1, Q2)	28.0 (24.2, 32.0)	29.6 (27.2, 32.5)	0.142
Waist circumference, cm, Me (Q1, Q2)	82 (75, 97)	83 (72, 101)	0.422
Smoking, %	10.0	19.0	0.190
Duration of AH, years, Me (Q1, Q2)	5 (2, 8)	5 (3, 10)	0.215
Family history of CAD, %	38.1	35.7	0.804
LVEF, %, Me (Q1, Q2)	65 (61, 67)	68 (64, 70)	0.048
Total cholesterol, mg/dL, Me (Q1, Q2)	181 (164, 205)	180 (160, 194)	0.563
Triglycerides, mg/dL, Me (Q1, Q2)	88 (82, 99)	86 (76, 103)	0.349
Creatinine, mg/dL, Me (Q1, Q2)	0.75 (0.74, 0.78)	0.78 (0.73, 0.82)	0.157
Blood glucose, mmol/L, Me (Q1, Q2)	5.3 (4.8, 5.6)	5.4 (4.8, 5.9)	0.168
Hemoglobin, g/L, Me (Q1, Q2)	131 (125, 138)	132 (124, 137)	0.634

The data are shown as Me (Q1, Q2). Mann-Whitney U test was used to compare the variables; AH - arterial hypertension; BMI - body mass index; CAD - coronary artery disease; E-M - enalapril and metoprolol; F-A - fosinopril and atenolol; LVEF - left ventricular ejection fraction; Q₁, Q₂ - interquartile ranges

(0.04-0.15 Hz) of HRV were analyzed and LF/HF ratio was calculated (6). VLF range was not included in our analysis to avoid questionable results, because we registered short-time ECG records (6).

To estimate synchronization between the 0.1-Hz rhythms in HR and PPG we used the method proposed by us recently (10, 19). Index S defines the relative time of synchronization between the considered 0.1-Hz rhythms.

Statistical analysis

We apply the Shapiro-Wilk test to check whether the data are approximately normally distributed. Since these data occur to be non-normal, their further analysis was carried out using non-parametric statistical methods. To compare the variables between patients' groups we used the Mann-Whitney test. To compare the variables within one patients' group we used the Wilcoxon test. Logistic regression was used for multiple analysis. Continuous variables are reported as medians (Me) with interquartile ranges (Q1, Q2) for non-normal data or mean (M) with standard deviation (σ) for normal data. Categorical data are presented as frequencies and percentages. The obtained estimations were considered statistically significant if $p < 0.05$. For a statistical analysis the software package Statistica 6.1 (StatSoft Inc., Tulsa, Oklahoma, USA) was used.

Receiver operating characteristics (ROC) curves and associated area under curve (AUC) were assessed for binary classifier system with continuous predictors. AUC is presented with its 95% confidence interval (CI), AUC (95% CI). Sensitivity (Se) and specificity (Sp) were also assessed and presented with its 95% CI.

The odds ratio (OR), χ^2 -index, Se and Sp were used to assess the ability of different autonomic control indices to correct the hypertensive therapy in AH patients.

Results

BP and antihypertensive treatment

F-A-patients had significantly lower BP levels than E-M-patients during all stages of our study ($p < 0.05$) (Table 2). The hypotensive effect of drug therapy was also more pronounced in F-A-patients (Table 2).

Table 2. Estimated BP in F-A and E-M-patients before and after two-week treatment with ACE-Is or β -blockers

	F-A-patients (n=63)				E-M-patients (n=42)			
	SBP, mm Hg	Δ_1 , mm Hg	DBP, mm Hg	Δ_2 , mm Hg	SBP, mm Hg	Δ_1 , mm Hg	DBP, mm Hg	Δ_2 , mm Hg
ACE-Is								
Before treatment	129 \pm 12	-11 \pm 8	83 \pm 8	-5 \pm 4	135 \pm 10 \diamond	-6 \pm 5 \diamond	87 \pm 8 \diamond	-7 \pm 9
After treatment	118 \pm 8*		77 \pm 7*		128 \pm 8 \diamond		80 \pm 6 \diamond	
β-blockers								
Before treatment	125 \pm 11	-9 \pm 6	82 \pm 8	-6 \pm 4	136 \pm 12 \diamond	-5 \pm 4 \diamond	85 \pm 9	-2 \pm 4 \diamond
After treatment	117 \pm 10*		75 \pm 8*		129 \pm 9 \diamond		83 \pm 7 \diamond	

The data are shown as $M \pm \sigma$;
DBP is the diastolic blood pressure, SBP is the systolic blood pressure; Δ_1 =[SBP after drug treatment]-[SBP before drug treatment]; Δ_2 =[DBP after drug treatment] - [DBP before drug treatment]; *-significant difference ($p < 0.05$) from parameter values before drug treatment (Wilcoxon test); \diamond -significant difference ($p < 0.05$) from the same parameter in F-A-patients (Mann-Whitney U test)

ACE-Is treatment and autonomic indices dynamics

Initially, values of index S in horizontal position of patient's body and power of HF band in HRV spectrum in both horizontal and vertical positions of patient's body were significantly greater in F-A-patients than in E-M-patients ($p < 0.05$) (Table 3). At the same time, both LF/HF ratio in horizontal position and HR were significantly greater in E-M-patients than in F-A-patients ($p = 0.002$) (Table 3).

The dynamics of index S and LF/HF ratio was similar under treatment with fosinopril and enalapril ($p > 0.05$). Enalapril increased the power of LF and HF bands in HRV spectrum and decreased the HR more often than fosinopril ($p < 0.05$) (Table 4). In E-M-patients we observed a significantly greater increase of LF and HF bands power (in vertical positions of patient's body) after ACE-Is treatment than in F-A-patients. However, the HR remains in average approximately constant in E-M-patients during the treatment. After the treatment with ACE-Is, the status of autonomic regulation in both groups of AH patients was similar ($p > 0.05$) (Table 5).

Cardio selective β -blockers and autonomic indices dynamics

After two-week break in drug therapy (i.e. two-week wash out period) the F-A-patients and E-M-patients had close values of parameters of CVS autonomic regulation. The values of index S, HR, power of LF and HF bands in all AH patients return to baselines values of F-A-patients (presented in F-A-patients column, Table 3) during the two-week break in drug therapy.

Atenolol and metoprolol had similar influence on ΔS ($p > 0.05$) (Table 4). Besides, atenolol and metoprolol had a comparable effect on HR, LF/HF ratio and the power of LF and HF bands (Table 4).

AH patients clusterization according to the effect of antihypertensive treatment on autonomic regulation

The dynamics of parameters of CVS autonomic regulation in AH patients was different under treatment (Table 4). One part of patients had improvement in their CVS autonomic control (positive effect), while another part of patients exhibited increased autonomic dysfunction of CVS (negative effect).

Table 3. Values of index S, HR, and power of LF and HF bands in HRV spectrum in groups of AH patients during a tilt test before the start of study

Parameter	Body's position	F-A-patients (n=63)	E-M-patients (n=42)	P level
S, %	horizontal	25 (19, 39)	20 (13, 25)	0.004
	vertical	21 (13, 29)	22 (16, 32)	0.478
LF, ms ²	horizontal	291 (145, 511)	230 (133, 460)	0.440
	vertical	315 (169, 567)	236 (92, 397)	0.053
HF, ms ²	horizontal	241 (107, 488)	110 (49, 215)	0.002
	vertical	123 (52, 240)	58 (29, 158)	0.013
LF/HF ratio	horizontal	1.28 (0.75, 1.98)	1.85 (1.24, 3.87)	0.002
	vertical	2.91 (1.37, 4.79)	3.25 (1.99, 4.95)	0.423
HR, min ⁻¹	horizontal	65 (59, 71)	73 (68, 78)	0.001
	vertical	80 (70, 89)	87 (80, 97)	0.002

The data are shown as Me (25%, 75%). Mann-Whitney U test was used to compare the variables

Table 4. Dynamics of index S, HR, and power of LF and HF bands in HRV spectrum in groups of AH patients under treatment with ACE-Is or β -blockers

Parameter	Body's position	F-A-patients (n=63)	E-M-patients (n=42)	P level
ACE-Is				
		fosinopril	enalapril	
Δ S, %	horizontal	-3 (-17, +13)	+1 (-14, +14)	0.463
	vertical	-2 (-15, +12)	-7 (-19, +12)	0.382
Δ LF, ms ²	horizontal	-64 (-182, +56)	+19 (-113, +182)	0.084
	vertical	-52 (-213, +82)	+26 (-60, +125)	0.020
Δ HF, ms ²	horizontal	-22 (-202, +93)	+21 (-76, +71)	0.226
	vertical	-19 (-91, +16)	+4 (-50, +75)	0.043
Δ LF/HF ratio	horizontal	-0.09 (-0.65, +0.59)	-0.01 (-0.59, +0.44)	0.850
	vertical	+0.10 (-0.70, +1.33)	+0.39 (-1.68, +1.52)	0.700
Δ HR, min ⁻¹	horizontal	+7 (+3, +14)	+1 (-7, +16)	0.029
	vertical	+12 (+4, +20)	-1 (-9, +11)	0.001
β-blockers				
		atenolol	metoprolol	
Δ S, %	horizontal	-1 (-15, +14)	+5 (-11, +13)	0.752
	vertical	-2 (-9, +7)	-3 (-14, +10)	0.874
Δ LF, ms ²	horizontal	+47 (-61, +142)	+90 (0, +197)	0.241
	vertical	+9 (-137, +170)	+54 (-36, +283)	0.090
Δ HF, ms ²	horizontal	+66 (-29, +279)	+20 (-27, +112)	0.236
	vertical	+20 (-16, +88)	+42 (-12, +102)	0.498
Δ LF/HF ratio	horizontal	-0.19 (-0.70, +0.13)	-0.36 (-0.93, +0.30)	0.933
	vertical	-0.64 (-1.43, +0.44)	-0.49 (-2.62, +0.38)	0.748
Δ HR, min ⁻¹	horizontal	-3 (-14, 0)	-9 (-19, 0)	0.092
	vertical	-14 (-22, 0)	-15 (-29, 0)	0.095

The data are shown as Me (25%, 75%). Mann-Whitney U test was used to compare the variables
 Δ = [parameter value after drug treatment]-[parameter value before drug treatment]
Me - medians

Table 5. Values of index S, HR, and power of LF and HF bands in HRV spectrum in groups of AH patients during a tilt test after treatment with ACE-Is (fosinopril or enalapril)

Parameter	Body's position	F-A-patients (n=63)	E-M-patients (n=42)	P level
S, %	horizontal	28 (22, 37)	27 (14, 40)	0.753
	vertical	25 (14, 32)	22 (15, 32)	0.996
LF, ms ²	horizontal	276 (107, 394)	274 (129, 690)	0.314
	vertical	223 (145, 481)	235 (139, 467)	0.679
HF, ms ²	horizontal	203 (92, 299)	157 (80, 304)	0.509
	vertical	90 (46, 170)	90 (38, 148)	0.955
LF/HF ratio	horizontal	1.29 (0.74, 1.86)	1.69 (1.21, 2.43)	0.042
	vertical	2.97 (1.76, 4.13)	3.43 (2.16, 5.00)	0.503
HR, min ⁻¹	horizontal	74 (66, 80)	76 (68, 87)	0.384
	vertical	93 (85, 101)	87 (81, 101)	0.101

The data are shown as Me (25%, 75%). Mann-Whitney U test was used to compare the variables
Me - medians

index S in horizontal and vertical body's positions has increased or not changed during treatment (positive effect). In this case the following conditions are fulfilled:

i) $(S_{ha} - S_{hb}) \geq 0$, where S_{ha} is the S value in the patient's body horizontal position after treatment and S_{hb} is the S value in the patient's body horizontal position before treatment,

ii) $(S_{va} - S_{vb}) \geq 0$, where S_{va} is the S value in the patient's body vertical position after treatment and S_{vb} is the S value in the patient's body vertical position before treatment.

In other cases we consider the changes of autonomic dysfunction in CVS as a negative effect.

Four groups of AH patients were identified on the basis of positive or negative effect of treatment with ACE-Is or β -blockers on autonomic dysfunction. AH patients with positive effect of treatment with ACE-Is or β -blockers on autonomic dysfunction were named as (ACE+) and (β +) patients, respectively. The groups named as (ACE-) and (β -) patients included AH patients with negative effect of treatment with ACE-Is inhibitors or

We consider as an improvement or not deterioration of systemic autonomic function in AH patients the case, where the

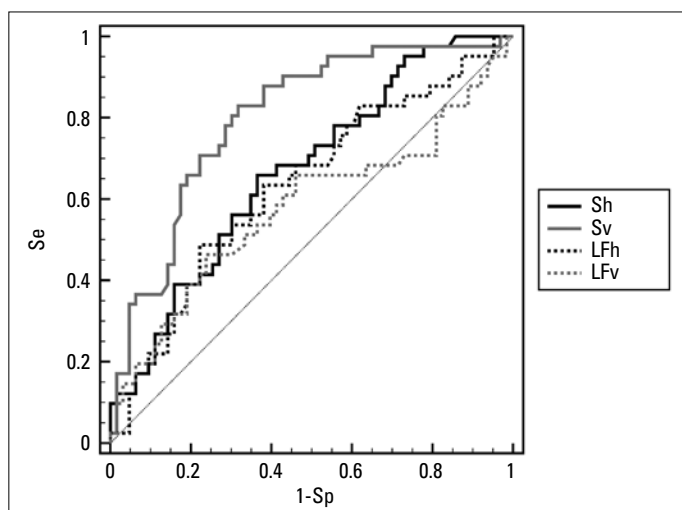


Figure 2. ROC curves for different critical values of index S and power of LF band in HRV spectrum before treatment as factors of positive effect of ACE-Is on 0.1-Hz rhythms synchronization in CVS

Note: Characteristics of AUC (Area under the Curve) are presented in Table 6

β -blockers, respectively. Thus, the following groups of AH patients were identified: (ACE+, β +), (ACE+, β -), (ACE-, β +) and (ACE-, β -). The effects of drugs were assessed independently to each other. All four identified groups had similar anthropometric characteristics.

This principle of separation of AH patients into groups is based on our assumption that optimal antihypertensive treatment should not reduce the index S of 0.1-Hz rhythms synchronization, since the target values of BP are achieved. Earlier we have shown that the increase of index S values is associated with the decrease of personal risk of cardiovascular events (21).

Evaluation of antihypertensive treatment effect on 0.1-Hz rhythms synchronization using initial values of autonomic indices

We have studied the possibility of predicting the effect of ACE-Is and β -blockers treatment on 0.1-Hz rhythms synchronization in CVS using the initial values of indicators of CVS autonomic regulation in AH patients. The discriminant analysis has shown the possibility of such prediction based on the initial values of index S ($p < 0.001$) and power of LF band in HRV spectrum ($p = 0.04$). Both parameters characterize the CVS autonomic regulation mechanisms generating 0.1-Hz oscillations in HR and PPG. The power of HF band in HRV spectrum was not important for the goal of our study ($p = 0.16$).

We analyzed the choice of critical value of index S and power of LF band in HRV spectrum before treatment, above which the effect of treatment with ACE-Is or β -blockers on synchronization of 0.1-Hz rhythms in HR and PPG may be considered as a positive one in AH patients from the viewpoint of correction of autonomic dysfunction in CVS.

Figure 2 displays a ROC curves for different critical values of S_h , S_v , LF_h , and LF_v before treatment with respect to evaluation of potential effect of ACE-Is treatment on index S dynamics, where S_h and S_v are the values of S in the horizontal and vertical

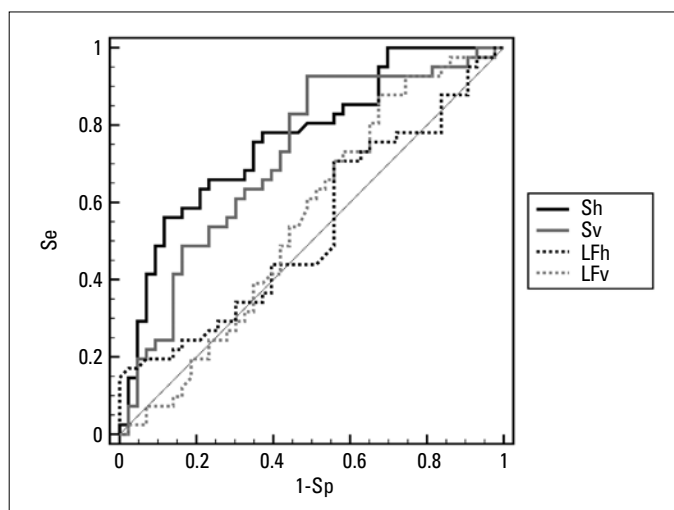


Figure 3. ROC curves for different critical values of index S and power of LF band in HRV spectrum before treatment as factors of positive effect of β -blockers on 0.1-Hz rhythms synchronization in CVS

Note: Characteristics of AUC (Area under the Curve) are presented in Table 6

position of patient's body, respectively, and LF_h and LF_v are the powers of LF band in HRV spectrum in the horizontal and vertical position of patient's body, respectively. A ROC graph depicts relative tradeoffs between benefits (true-positives) and costs (false-positives). An optimal point in ROC curve is the one that has high true-positive rate plotted on the Y-axis and low false positive rate plotted on the X-axis. As the optimal relationship between Se and Sp of S and power of LF band as the factors of high positive effect of ACE-Is on 0.1-Hz rhythms synchronization in CVS we choose the following: $LF_h > 250 \text{ ms}^2$ [$\chi^2 = 9.8$, $p = 0.003$; OR=3.9 (95% CI 1.6-9.7), Se=52%, Sp=78%] and $S_v < 25\%$ [$\chi^2 = 17.9$, $p = 0.0005$; OR=10.2 (95% CI 3.0-38.3), Se=90%, Sp=52%].

Figure 3 shows ROC curves for different critical values of S and power of LF band before treatment with respect to evaluation of potential effect of treatment with β -blockers on index S dynamics. As the optimal relationship between Se and Sp of S and power of LF band as factors of high positive effect of β -blockers on 0.1-Hz rhythms synchronization in CVS we choose: $LF_v < 350 \text{ ms}^2$ [$\chi^2 = 4.2$, $p = 0.04$; OR=1.8 (95% CI 0.6-4.9), Se=73%, Sp=40%] and $S_v < 30\%$ [$\chi^2 = 15.8$, $p = 0.0006$; OR=12.1 (95% CI 2.9-57.99), Se=93%, Sp=49%].

Characteristics of AUC are presented in Table 6 for Figures 2 and 3.

We studied the possibility of joint use of the critical values of S and power of LF band for the differentiated prescription of antihypertensive drug. The joint criteria of $LF_h > 250 \text{ ms}^2$ and $S_v < 25\%$ provides a good estimate of positive effect of ACE-Is on 0.1-Hz rhythms synchronization in HR and PPG [$\chi^2 = 12.2$, $p = 0.001$; OR=4.7 (95% CI 1.9-12.0), Se=60%, Sp=76%]. The joint criteria of $LF_v < 350 \text{ ms}^2$ and $S_v < 30\%$ provides a good estimate of positive effect of β -blockers on 0.1-Hz rhythms synchronization in CVS [$\chi^2 = 12.2$, $p = 0.001$; OR=5.6 (95% CI 2.0-16.0), Se=71%, Sp=69%].

Note that ACE-Is and β -blockers provide equally positive effect on dynamics of 0.1-Hz rhythms synchronization in HR and

Table 6. Characteristics of AUC (Area under the curve) of ROC curves from Figures 2 and 3

Parameter	ACE-Is treatment (Fig.2)	P-level for β -blockers treatment (Fig.3)
S_h	AUC=0.676 (0.578-0.764), $P<0.001$	AUC=0.765 (0.660-0.851), $P<0.001$
S_v	AUC=0.800 (0.710-0.872), $P<0.001$	AUC=0.718 (0.609-0.810), $P<0.001$
LF_h	AUC=0.633 (0.534-0.725), $P=0.017$	AUC=0.535 (0.422-0.644), $P=0.590$
LF_v	AUC=0.578 (0.478-0.675), $P=0.199$	AUC=0.554 (0.442-0.663), $P=0.367$
The data are shown as AUC (95% CI)		

PPG in 20% of AH patients. These patients were named as (ACE+, β +) patients. They had lower initial values of index S during a tilt test than other patients. In particular, $S_h=19$ (14, 24)% and $S_v=18$ (13, 26)% in (ACE+, β +) patients vs $S_h=24$ (16, 35)% ($p=0.009$) and $S_v=22$ (15, 35)% ($p=0.01$), respectively, in (ACE+, β -) and (ACE-, β +) patients.

(ACE-, β -) patients (25% of general group) had higher initial values of index S during a tilt test than other AH patients. In particular, $S_h=30$ (24, 44)% and $S_v=27$ (18, 34)% in (ACE-, β -) patients vs. $S_h=22$ (15, 33)% ($p=0.005$) and $S_v=20$ (14, 30)% ($p=0.03$), respectively, in (ACE+, β +) patients, (ACE+, β -) patients, and (ACE-, β +) patients.

The total Se and Sp of our method was 65% and 73%, respectively [$\chi^2=26.9$, $p=0.0005$; OR=5.2 (95% CI 2.7-10.2)].

We found no dependence of the dynamics of index S values on the dynamics of BP levels in F-A-patients and E-M-patients.

Thus, the AH patients with $S<25\%$ in vertical body's position and $LF>250$ ms² in horizontal body's position require ACE-Is treatment. The AH patients with $LF<350$ ms² and $S<30\%$ in vertical body's position require β -blocker treatment. The AH patients with $S>25\%$ and $LF>250$ ms² in horizontal body's position do not require any ACE-Is or β -blocker treatment. Both drug groups can be used in patients with low values of index S and low power of LF band in HRV spectrum.

Discussion

Initial difference on index S , HF band in HRV spectrum and LF/HF ratio between the groups of AH patients (Table 3) may be caused by their difference in BP (Table 2). This fact is probably a casual bias in randomization. We consider this bias in the following results interpretation as limitation, because this initial difference in the status of autonomic regulation in the groups of AH patients may be associated with the difference between the effect of fosinopril and enalapril on dynamics of some autonomic indices (LF and HF bands in HRV spectrum, HR) (Table 4).

We did not study the difference between the effects of atenolol and metoprolol on autonomic indices considered by us. Study results on fosinopril and enalapril are mixed. Detailed comparison of drugs efficacy (fosinopril vs. enalapril, atenolol vs.

metoprolol) was not the aim of this study, due to a number of study limitations (see Study limitations section). However, the identified individual effect of ACE-Is and β -blockers treatment on autonomic regulation of CVS formed the basis for a new approach, described below.

We have proposed a new approach to control of antihypertensive treatment in AH patients, which is based on individual features of autonomic dysfunction in CVS. The power of LF band in HRV spectrum and index S of synchronization of 0.1-Hz rhythms in ECG and PPG can be used as criteria for initial assessment of autonomic regulation in AH patients.

The introduced index S of synchronization between the 0.1-Hz rhythms in HR and PPG characterizes the quality of functional interaction between the subsystems of CVS. It is known that blood flow in skin microcirculation is an indicator of status of blood flow in main arteries (41). The status of 0.1-Hz regulation of HR is defined by the power of LF band in HRV spectrum.

Basing on the obtained results, we believe that ACE-Is or β -blockers treatment should not be used in AH patients with a good quality of functional interaction between 0.1 Hz-regulation of HR and PPG, which manifests itself as $S>25\%$ and $LF>250$ ms².

ACE-Is are recommended for AH patients with poor quality of functional interaction between the 0.1-Hz rhythms in HR and PPG ($S_v<25\%$) and satisfactory quality of baroreflex regulation of heart ($LF_h>250$ ms²). β -blockers are recommended for AH patients with systemic autonomic dysfunction in CVS ($S_v<30\%$) and dysfunction of heart 0.1-Hz regulation ($LF_v<350$ ms²).

Note that values of index S during a tilt test are useful for the assessment of the positive effect of drug treatment in AH patients. It could be explained possibly by the fact that systemic autonomic dysfunction in CVS is more pronounced during a tilt test.

Our results complement the knowledge of AH pathogenesis. It is known that AH is characterized not only by an increase in sympathetic nervous system activity (28, 29, 40), reduced vagal modulations of the sinoatrial node (43) and blunted baroreflex gain (18), but also by systemic autonomic dysfunction in CVS, which manifests itself as a desynchronization of 0.1-Hz rhythms in HR and PPG.

Some studies have shown that the progressive increase of power of LF band in HRV spectrum with the increase of AH heaviness and the decrease of this power as the result to a tilt test agree well with the known impairment in baroreflex gain at AH (44). The origin of 0.1-Hz oscillations in HRV is still a subject of controversy. These oscillations are probably the result of the combined vagal and sympathetic activity (17) providing baroreflex regulation. We found out that the increase in power of LF band is observed not in all AH patients. Some patients show a decrease of LF band power in HRV spectrum with the overall reduction of HRV. It may be the result of severe systemic autonomic dysfunction in CVS with damage of heart regulation, which can take place in severe hypertension (45).

In this study we have shown that vagal impact characterized by the power of HF band in HRV spectrum (43, 46) is not

significant for the assessment of autonomic system dysfunction in CVS. Therefore, we have not used it for antihypertensive treatment control in AH patients. It should be noted that autonomic dysfunction is an important prognostic factor for evaluation of the risk of cardiovascular events in patients after myocardial infarction and patients with chronic heart failure (21, 47, 48). However, its prognostic value for evaluation of the risk of cardiovascular events is not proved for AH patients (39, 40). But we believe that the antihypertensive treatment control should take into account individual features of autonomic dysfunction in CVS of AH patients. The use of antihypertensive drugs enhancing individual autonomic dysfunction (ACE-Is or β -blockers in AH patients with specific value of *S* index and power of LF band as indicated above) is undesirable because it can potentially worsen the prognosis of AH or promote the concomitant diseases. Note that the critical values of *S* in AH patients (25% in horizontal position), showed in this study, are close to the prognostic critical *S* level in myocardial infarction patients (20%), showed in (21).

Se and Sp of the presented approach to AH treatment control is not very high (<80%). But the use of index *S* and power of LF band in HRV spectrum may be potentially perspective as additional criteria for AH treatment control.

Study limitations

Our study included only 105 AH patients. It is a rather small sample, but our study was a prospecting one, which can give rise to more representative investigations of synchronization index *S* potential for antihypertensive treatment control. Besides, we used a number of criteria to enroll the patients in the study and to exclude them from the study (see the Methods section).

At the beginning of the study, BP level was below 140/90 mm Hg in most AH patients (Table 2), despite 7 days absence of prior antihypertensive treatment. This fact is casual in our study and may be caused by residual effect of prior antihypertensive treatment on BP. Relationship between BP and autonomic dysfunction has not been studied now. Initial low BP level can limit our results for AH patients with high initial BP.

Initial BP in F-A and E-M groups were different because probably a casual bias in randomization. This fact may be associated with some initial group-specific singularities of autonomic regulation and ACE-Is effect on it.

The absence of a control group of hypertensive patients is a limitation of our study.

Note that our results are applicable for some drugs only (fosinopril, enalapril, atenolol and metoprolol). Applicability of our results to other ACE-Is and β -blockers requires further study. The rationale for the drugs used in the two treatments sequences is debatable. We used the available drugs in our clinic. We had no other preference in the choice of drugs for this study.

In our study we compared the 2 groups of patients. But we have consistently used ACE-Is and β -blockers for each group (F-A and E-M). Detailed comparison of clinical efficacy of drugs

(for example, fosinopril vs. enalapril, atenolol vs. metoprolol) was not the aim of this study. We did not study the individual Se of patients to drugs, determined by various factors (genetic and metabolic factors, beta adrenergic receptorial Se, etc.), thus we cannot assess equal individual effective doses of drugs. It is the main limitation of the study.

At present, it is unknown whether "better" values of LF band or *S* index achieved by a certain drug translate into a clinical benefit for AH patients. Therefore, our results are of limited value in clinical cardiology now, but it could be the basis for future clinical studies.

Conclusion

In our study we revealed that assessment of index *S* of synchronization of 0.1-Hz rhythms in HR and PPG and the power of LF band in HRV spectrum have a great potential for control of the cardiovascular risk based on individual features of autonomic dysfunction in CVS under antihypertensive treatment in AH patients.

It is shown that ACE-Is are recommended for AH patients with initial poor quality of functional interaction between the 0.1-Hz rhythms in HR and PPG and satisfactory quality of baroreflex heart regulation. β -blockers are recommended for AH patients with systemic autonomic dysfunction in CVS and dysfunction of heart 0.1-Hz regulation. Both of these drugs can be used in patients with poor quality of 0.1-Hz rhythms synchronization in CVS and baroreflex heart regulation. In AH patients with a good quality of functional interaction between the 0.1-Hz rhythms in HR and PPG these drugs are not recommended.

Se and Sp of our approach were 65% and 75%, respectively.

Despite many study limitations and moderate levels of Se and Sp we believe that the results of our study are of interest as perspective for future research on AH treatment control.

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