Autonomic control of cardiovascular system in pre- and postmenopausal women: a cross-sectional study

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Abstract

Objective: The aim of this cross-sectional study was to assess the features of autonomic control of the cardiovascular system in pre- and post-menopausal women.

Material and Methods: We studied 185 postmenopausal women aged 59.3±8.5 years (mean±SD) and 104 premenopausal women aged 45.1±5.8 years. Standard indices of heart rate variability (HRV) (mean heart rate, coefficient of variation, standard deviation of the NN interval (the time elapsing between two consecutive R waves in the electrocardiogram with normal sinus rhythm) (SDNN), square root of the mean squared differences of successive NN intervals (RMSSD), proportion derived by dividing RR50, the number of interval differences of successive NN intervals greater than 50 ms, by the total number of NN intervals (PNN50), and power of low frequency (LF) and high frequency (HF) bands in absolute values and percentages of total spectral power) and index S of synchronization between the 0.1-Hz rhythms in heart rate and pho-toplethysmogram were compared between these two groups at rest. We assessed the following sex hormones: estradiol, follicle stimulating hormone, dehydroepiandrosterone sulfate, and testosterone.

Results: Mean heart rate and power of LF and HF bands were significantly different (p<0.05) in pre- and postmenopausal women. The autonomic indices were similar in women with natural and surgical menopause. Some indices (coefficient of variation, SDNN, RMSSD, PNN50, and power of LF and HF bands) showed weak correlation with menopause time in women with natural menopause. In women with surgical menopause, a moderate statistically significant correlation was observed only between menopause time and S index (r=-0.41, p=0.039). In premenopausal women, only testosterone correlated weakly with coefficient of variation, SDNN, PNN50, RMSSD, and power of HF band. In postmenopausal women, no correlations were found. We did not find any significant relationship between autonomic indices and hot flashes, assessed by hot flash diary.

Conclusion: We did not find a clinically important relationship between cardiovascular autonomic control and menopausal status in women. (J Turk Ger Gynecol Assoc 2015; 16: 11-20)

Keywords: Autonomic control, menopause, heart rate variability, 0.1-Hz rhythms, sex hormones, hot flashes

Introduction

The effect of menopause on cardiovascular disease (CVD) in women has been studied by Kannel et al. (1). It has been found that autonomic dysfunction is an important factor for the evaluation of risk of cardiovascular events in CVD patients (2, 3). Age-related changes in autonomic control of the cardiovascular system (CVS) are also well known (2, 4-6). The difference of heart rate variability (HRV) indices in pre- and postmenopausal women has been reported (7, 8). Vongpatanasin W. has studied the increase of sympathetic tone and blood pressure in menopause (9). Lee et al. (10)

have found a relationship between menopausal symptoms and changes in cardiovascular autonomic regulation in women. For example, hot flashes and sleep disorders are strongly associated with increased sympathetic tone (10). Moreover, a significant decrease in cardiac vagal control occurs during hot flashes (11). These signs of autonomic dysfunction may be important for cardiovascular risk assessment. The influence of sex hormones, in particular, hormone replacement therapy (HRT), on cardiovascular autonomic control is controversial (8, 12-17). Moreover, several authors reported the influence of body mass index (BMI) on autonomic control in women (18).

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Autonomic control in CVS can be assessed by HRV analysis. Various time domain and frequency domain indices are usually used for this purpose (2). The physiological explanation of these indices is known (2, 19, 20). These indices can assess cardiac autonomic regulation but not peripheral blood flow. In our previous papers, we have proposed an original method for the assessment of cardiovascular autonomic control based on synchronization between the 0.1-Hz rhythms in heart rate (HR) and photoplethysmogram (PPG) (21). The quality of 0.1-Hz rhythms synchronization was found to be higher in healthy subjects than in patients with cardiovascular disease (22). From a physiological viewpoint, the synchronization of 0.1-Hz rhythms is the result of adequate functional interaction of CVS parts (heart and peripheral vessels). The clinical importance of this diagnostic method is shown for patients with prior myocardial infarction, patients with acute coronary syndrome, and hypertensive patients (3, 23).

The physiological explanation of 0.1-Hz rhythms in PPG is a debatable point. An opto-physiological model of a finger in conjunction with a near-infrared reflectance PPG device has been proposed (24). It was shown that both oscillations in the microcirculatory bed and blood filling of digital arteries make a substantial contribution to the PPG signal. Therefore, 0.1-Hz oscillations in PPG may be associated directly with baroreceptor regulation of blood pressure (BP). At the same time, a number of authors assume that 0.1-Hz oscillations in blood microcirculation are not associated with autonomic regulation (25-28). To avoid confusion, we do not interpret the origin of 0.1-Hz oscillations in PPG in the present paper.

Thus, the features of cardiovascular autonomic control in women before and after menopause are not fully understood. Controversial results concerning this problem have been reported. The aim of the present study cross-sectional study is to assess the features of autonomic control of CVS in pre- and postmenopausal women.

Material and Methods

Patients

The study was approved by the ethics committee of the Saratov Research Institute of Cardiology in Saratov, Russia (no. 24, Sept. 12, 2013) and informed consent was obtained from all participants.

Our cross-sectional study included 185 postmenopausal women aged 59.3±8.5 years (mean±SD) and 104 premenopausal women aged 45.1±5.8 years. Both groups were investigated and treated, if necessary, in the clinic of Saratov State Medical University (Saratov, Russia). Clinical characteristics (cardiovascular, gynecological, etc.) were assessed in all women. We assessed the level of the following sex hormones: estradiol, follicle-stimulating hormone (FSH), dehydroepiandrosterone sulfate (DHEAS), and testosterone. Only patients aged between 35 and 70 years were enrolled in our study. Women with CVD were not on beta-blockers or calcium channel blockers during the 7 days before the start of the study.

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

i) valvular defect of the heart
ii) rhythm other than sinus that would impede analysis of HRV
iii) endocrine pathology, excluding diabetes mellitus
iv) chronic gastrointestinal diseases (hepatitis, gastric ulcer, duodenum disease, and cholecystitis), chronic diseases of the kidneys, and other chronic diseases in the stage of exacerbation

Signal recording

To examine the autonomic control of the CVS, we carried out HRV analysis and estimated the degree of synchronization between the 0.1-Hz rhythms in HR and PPG. PPG, measured on the middle finger of the subject's hand; electrocardiogram (ECG); and respiration were simultaneously recorded at rest. The signals were recorded within 10 minutes in the supine position.

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

Signal processing

We analyzed HRV in the frequency domain and time domain using HR and PPG signals simultaneously recorded within 10 minutes. We evaluated the following time domain HRV parameters: mean heart rate (mean HR), standard deviation of the NN interval (the time elapsing between two consecutive R waves in the electrocardiogram with normal sinus rhythm) (SDNN), coefficient of variation (CV), square root of the mean squared differences of successive NN intervals (RMSSD), and proportion derived by dividing NN50-the number of interval differences of successive NN intervals greater than 50 ms-by the total number of NN intervals (PNN50) (2).

High-frequency (HF) range, 0.15-0.4 Hz, and low-frequency (LF) range, 0.04-0.15 Hz, of HRV were analyzed (2). Power of LF and HF bands in the HRV power spectrum was presented in absolute values (ms^2) and in percentage of total spectral power (LF% and HF%). LF /HF ratio was also calculated (2). Very-low-frequency range of HRV was not included in our analysis to avoid questionable results, because we registered short-time ECG records (2).

To estimate synchronization between the 0.1-Hz rhythms in HR and PPG, we used the method proposed by us recently (21). Index S defines the relative time of synchronization between the 0.1-Hz rhythms considered.

Statistical analysis

Continuous variables are reported as medians with interquartile ranges, Me (Q1, Q3). Categorical data are presented as frequencies and percentages. The obtained estimations were considered statistically significant if $p < 0.05$. For the statistical analysis, the software package Statistica 6.1 (StatSoft Inc., Tulsa, Oklahoma, USA) was used.

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We applied the Shapiro-Wilk test to check whether the data were approximately normally distributed. Since these data were non-normal, their further analysis was carried out using non-parametric statistical methods. To compare the variables between patient groups, we used the Mann-Whitney test. To compare the variables within one patient group, we used the Wilcoxon test. Paired relationships between continuous variables were assessed using Spearman correlation coefficients (0.68-1.0 is high correlation, 0.36-0.67 is moderate correlation, and ≤0.35 is low correlation (29). For categorical variables, chi-square (χ^2) test was used to estimate their relationships. Multiple regression analysis with sigma-restricted parameterization was used to study multivariate effects for continuous and categorical variables.

Discriminant analysis was used to determine the set of studied parameters (clinical status, sex hormones, and cardiovascular autonomic indices) that resulted in the best separation of groups of women with hot flashes and without them.

Receiver operating characteristics (ROC) curves and corresponding area under curve (AUC) values were assessed for the binary classifier system with continuous predictors. AUC is presented with its 95% confidence interval (CI). We also assessed sensitivity (Se) and specificity (Sp) and presented them with their 95% confidence interval.

Results

Menopause, clinical status, and sex hormones
The clinical characteristics of the pre- and postmenopausal women are presented in Table 1. Postmenopausal women had a greater frequency of hot flashes assessed by hot flash diary, angina pectoris, arterial hypertension, and diabetes mellitus than premenopausal women. We revealed a strong relationship between the level of sex hormones (estradiol, testosterone, FSH, and DHEAS) and menopause (AUC tends to 1.0).

In the postmenopausal group, natural and surgical menopause occurred in 161 and 26 women, respectively. The clinical characteristics of these subgroups are presented in Table 2. Women with surgical menopause were younger than other postmenopausal women and had a greater frequency of hot flashes, greater levels of FSH and DHEAS, and lower levels of estradiol and testosterone. Also, 4.4% and 7.7% of women with natural and surgical menopause, respectively, received hormone replacement therapy. Exclusion of these patients from consideration did not change the observed differences in sex hormone levels between the subgroups studied. Menopause time was similar in women with natural and surgical menopause (Table 2).

We constructed a discriminant model based on sex hormones, age, HRT (binary), CVD (binary), and BMI for prediction of hot flashes separately in pre- and postmenopausal women. In premenopausal women, the constructed discriminant model had *Wilks' lambda* =0.72 and *approximate* F (8.98)=4.74 (p<0.001). The percent of correctly classified cases using the constructed model was 50.0% for women with hot flashes and 88.8% for women without hot flashes. Summary statistics for all variables of the model are presented in Table 3. The construct-

ed model showed low discriminatory power (*Wilks' lambda* >0.5 for each variable and for the model on the whole). The main predictor of hot flashes was FSH.

In postmenopausal women, the constructed discriminant model had *Wilks' lambda*=0.55 and *approximate* F (8.17)=17.81 (p<0.001). The percent of correctly classified cases using the constructed model was 82.8% for women with hot flashes and 82.1% for women without hot flashes, respectively. Summary statistics for all variables of the model are presented in Table 3. The main predictors of hot flashes were estradiol and age. We did not find any relationship between smoking and sex hormones (p>0.1).

Correlations across cardiovascular autonomic indices
Many autonomic indices in our study correlated between themselves. Time domain indices (SDNN, CV, RMSSD, and PNN50) correlated strongly between themselves and with some frequency domain indices, but they did not correlate with HR, LF%, and *S* index. For example, SDNN had a Spearman correlation coefficient r>0.8, p<0.001 with all autonomic indices, excluding HR (r=-0.29, p<0.001), LF% (r=0.02, p=0.767), and *S* index (r=-0.22, p=0.003).

HR, LF%, and *S* index were the most independent autonomic indices in our study. We did not find any correlation between them (r<0.1, p>0.05 for all pairs). This observation was confirmed by multiple regression analysis, where adjusted R^2 took values from 0.12 to 0.15 in models for HR, LF%, and *S* index.

Menopause and cardiovascular autonomic indices
Most frequency domain and time domain parameters of cardiovascular autonomic control, excluding mean HR, were similar in pre- and postmenopausal women (Table 1). Mean HR was greater in premenopausal women. For classification of pre- and postmenopausal women, the optimal point of HR was 70 beats/min: Se=72.1% (95% CI=62.5-80.5), Sp=45% (95% CI=38.1-52.9), and AUC=0.589 (95% CI=0.530-0.646).

After the exclusion of patients with CVD (coronary heart disease, myocardial infarction, hypertension, stroke, and diabetes mellitus) from the analysis, the difference between pre- and postmenopausal women was additionally identified using the absolute values of LF and HF bands of the HRV spectrum and RMSSD (Table 1). Healthy premenopausal women had lower values of LF and HF than premenopausal women with CVD. On the contrary, healthy postmenopausal women were characterized by greater values of these indices than CVD patients. We did not reveal a significant difference in autonomic parameters in women with natural and surgical menopause (Table 2).

We also studied the correlation between cardiovascular autonomic indices and menopause time in women with natural and surgical menopause, including CVD patients (Table 4). It was shown that time domain indices (SDNN, CV, RMSSD, and PNN50) and some frequency indices (HF, HF%, and LF) correlated with menopause time in women with natural menopause (p<0.05). But, the values of these correlations were low. In women with surgical menopause, a moderate statistically significant correlation was observed only between menopause

Table 1. Clinical characteristics and cardiovascular autonomic indices in pre- and postmenopausal women

Parameters	Premenopausal (n=104) *(n=71)	Postmenopausal (n=187) *(n=55)	p
Age, years	46 (41, 49)	60 (53, 65)	<0.001
Hot flashes	13.6%	57.8%	<0.001
Estradiol, pmol/L	133 (121, 146)	74 (68, 84)	<0.001
FSH, IU/L	27 (24, 37)	80 (73, 85)	<0.001
Testosterone, nmol/L	1.7 (1.3, 2.0)	1.3 (1.1, 1.5)	<0.001
DHEAS, nmol/L	2.0 (1.2, 2.1)	5.7 (4.8, 5.9)	<0.001
HRT	1.9%	4.9%	0.208
Height, m	1.64 (1.60, 1.67)	1.63 (1.59, 1.65)	0.096
Waist, kg	73 (64, 86)	72 (66, 84)	0.452
BMI, kg/m^2	26.5 (24.2, 31.4)	27.1 (25.1, 31.6)	0.155
SBP, mmHg	120 (110, 135)	135 (120, 140)	0.021
DBP, mmHg	80 (70, 100)	90 (80, 100)	0.035
CHD, angina pectoris	6.7%	29.9%	<0.001
Prior myocardial infarction	0	2.7%	0.089
Arterial hypertension	26.9%	55.4%	<0.001
Prior stroke	0	2.2%	0.131
Diabetes mellitus	0	8.2%	0.032
Smoking	8.7%	6.0%	0.392
Mean HR, beats/min	75 (69, 82) *73 (69, 83)	72 (65, 80) *72 (66, 77)	0.012 *0.077
SDNN	32.8 (24.0, 48.9) *32.4 (23.4, 44.7)	33.7 (24.9, 53.9) *33.7 (24.3, 58.2)	0.371 *0.198
CV, %	4.0 (2.8, 6.0) *3.9 (2.8, 5.5)	4.1 (2.9, 6.6) *4.1 (2.9, 7.3)	0.604 *0.282
RMSSD	23.1 (13.3, 42.9) *20.9 (13.2, 41.6)	27.3 (16.4, 58.0) *26.1 (17.1, 57.9)	0.080 *0.048
PNN50	1.5 (0.2, 6.2) *1.3 (0.2, 3.9)	2.3 (0.3, 9.5) *1.9 (0.2, 11.2)	0.159 *0.309
HF, ms^2	75.2 (29.7, 204.2) *68.1 (28.9, 169.2)	102.1 (33.4, 434.5) *88.2 (50.4, 665.4)	0.055 *0.037
LF, ms^2	106.9 (54.8, 225.7) *98.5 (53.2, 188.8)	116.3 (57.8, 456.8) *143.4 (65.3, 456.8)	0.277 *0.043
HF, %	23.7 (10.2, 40.7) *21.0 (10.1, 41.5)	26.8 (14.6, 41.0) *25.1 (15.2, 38.6)	0.091 *0.301
LF, %	27.9 (20.9, 35.1) *26.7 (20.3, 34.2)	28.0 (18.2, 40.9) *28.1 (19.9, 41.6)	0.793 *0.409
S, %	46.9 (40.3, 55.9) *47.9 (40.2, 57.3)	43.6 (34.1, 55.3) *42.3 (31.3, 55.0)	0.087 *0.064

Continuous variables are presented as medians with inter-quartile ranges, Me (Q1, Q3). Categorical data are presented as percentages. FSH: follicle stimulating hormone; DHEAS: dehydroepiandrosterone sulfate; HRT: hormone replacement therapy; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; CHD: coronary heart disease; HR: heart rate; SDNN: standard deviation of the NN interval (the time elapsing between two consecutive R waves in the electrocardiogram with normal sinus rhythm); CV: coefficient of variation; RMSSD: square root of the mean squared differences of successive NN intervals; PNN50: proportion derived by dividing NN50: the number of interval differences of successive NN intervals greater than 50 ms, by the total number of NN intervals; HF: high frequency band in absolute values (ms^2); LF: low frequency band in absolute values (ms^2); HF%: high frequency band in percentage of total spectral power; LF%: low frequency band in percentage of total spectral power; S: Index S of synchronization between the 0.1-Hz rhythms
*Data in patients without CVD (CHD, hypertension, history of stroke, diabetes mellitus)

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Table 2. Clinical characteristics and cardiovascular autonomic indices in women with natural and surgical menopause

Parameters	Natural menopause (n=161)	Surgical menopause (n=26)	p
Age, years	60 (54, 65)	48 (45, 60)	<0.001
Hot flashes	52.8%	92.3%	0.001
Estradiol, pmol/L	74 (68, 85)	68 (57, 74)	<0.001
FSH, IU/L	78 (70, 83)	87 (83, 88)	<0.001
Testosterone, nmol/L	1.3 (1.1, 1.6)	1.1 (0.9, 1.2)	0.024
DHEAS, nmol/L	5.5 (4.4, 5.8)	5.9 (5.8, 6.1)	<0.001
Menopause time, years	9 (3, 16)	11 (4, 19)	0.787
HRT	4.4%	7.7%	0.789
Height, m	1.63 (1.60, 1.65)	1.64 (1.58, 1.65)	0.128
Waist, kg	73 (66, 84)	67 (64, 86)	0.191
BMI, kg/m^2	27.3 (25.7, 31.6)	25.8 (24.2, 32.0)	0.233
SBP, mmHg	140 (120, 150)	120 (115, 160)	0.054
DBP, mmHg	90 (80, 100)	80 (75, 100)	0.526
CHD, angina pectoris	30.6%	26.9%	0.765
Prior myocardial infarction	3.2%	0	0.799
Arterial hypertension	56.2%	53.8%	0.847
Prior stroke	2.5%	0	0.841
Diabetes mellitus	6.9%	19.2%	0.316
Smoking	3.8%	23.1%	0.115
HR, beats/min	72.6 (65.2, 80.1)	71.8 (66.0, 75.8)	0.567
SDNN, ms	33.7 (24.9, 61.2)	35.0 (24.3, 44.0)	0.533
CV, %	4.3 (2.9, 6.9)	3.9 (3.0, 6.2)	0.486
RMSSD, ms	27.3 (16.3, 59.5)	27.3 (16.5, 44.3)	0.548
PNN50	2.3 (0.4, 9.5)	2.1 (0.5, 9.5)	0.766
HF, ms^2	102.1 (34.0, 665.4)	69.1 (33.1, 204.2)	0.317
LF, ms^2	127.8 (60.8, 456.8)	105.1 (56.3, 285.2)	0.528
HF, %	26.8 (14.7, 41.0)	23.9 (13.7, 38.3)	0.483
LF, %	28.0 (18.2, 40.9)	27.8 (18.7, 43.2)	0.781
S, %	45.2 (33.3, 55.7)	37.5 (34.7, 46.8)	0.084

Continuous variables are presented as medians with inter-quartile ranges, Me (Q1, Q3). Categorical data are presented as percentages. FSH: follicle stimulating hormone; DHEAS: dehydroepiandrosterone sulfate; HRT: hormone replacement therapy; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; CHD: coronary heart disease; HR: heart rate; SDNN: standard deviation of the NN interval (the time elapsing between two consecutive R waves in the electrocardiogram with normal sinus rhythm); CV: coefficient of variation; RMSSD: square root of the mean squared differences of successive NN intervals; PNN50: proportion derived by dividing NN50: the number of interval differences of successive NN intervals greater than 50 ms, by the total number of NN intervals; HF: high frequency band in absolute values (ms^2); LF: low frequency band in absolute values (ms^2); HF%: high frequency band in percentage of total spectral power; LF%: low frequency band in percentage of total spectral power; S: Index S of synchronization between the 0.1-Hz rhythms

time and *S* index (Spearman r=-0.41, p=0.039). The absence of a statistically significant correlation with other autonomic indices may probably be explained by the small number of patients in this subgroup.

Multiple regression analysis did not reveal a significant relationship between cardiovascular autonomic indices and menopause time. We did not find a relationship between autonomic indices and BMI in pre- and postmenopausal women, including CVD patients (p>0.05).

Sex hormones and cardiovascular autonomic indices
In our study, the correlation between cardiovascular autonomic indices and some sex hormones (FSH and testosterone) was similar to the correlation observed between the autonomic indices and menopause time. The data from all patients, including CVD patients, were analyzed.

Some cardiovascular autonomic indices showed a low correlation (Spearman r<0.18, p<0.05) with a number of sex hormones in the whole group (n=289):

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Table 3. Summary statistics for all variables in the discriminant models for classification of women into two groups (with hot flashes and without hot flashes) based on sex hormones

No.		Variables	Wilks' Lambda	Partial Lambda	F-remove	p-level	Tolerance
Premenopausal women							
1		FSH*	0.76	0.95	4.80	0.031	0.15
2		Estradiol	0.75	0.97	3.37	0.069	0.16
3		Age	0.74	0.97	2.11	0.150	0.37
4		DHEAS	0.73	0.98	1.44	0.233	0.31
5		CVD	0.73	0.98	1.31	0.256	0.80
6		Testosterone	0.72	0.99	0.47	0.496	0.12
7		BMI	0.72	0.99	0.44	0.508	0.82
8		HRT	0.72	0.99	0.17	0.684	0.85
Postmenopausal women							
1		Estradiol*	0.79	0.69	78.08	<0.001	0.87
2		Age*	0.56	0.97	4.66	0.032	0.58
3		Testosterone	0.56	0.98	3.17	0.076	0.11
4		FSH	0.56	0.98	2.85	0.093	0.16
5		BMI	0.55	0.99	0.88	0.347	0.87
6		DHEAS	0.55	0.99	0.79	0.373	0.19
7		HRT	0.55	0.99	0.49	0.480	0.93
8		CVD	0.55	0.99	0.18	0.672	0.87

*Main predictor. FSH: follicle stimulating hormone; DHEAS: dehydroepiandrosterone sulfate; CVD: cardiovascular disease; BMI: body mass index; HRT: hormone replacement therapy

Table 4. Correlation of menopause time with sex hormone levels and cardiovascular autonomic indices

Parameters	Natural menopause (n=161)		Surgical menopause (n=26)	
	Spearman r	p	Spearman r	p
HR, beats/min	-0.03	0.717	-0.20	0.347
SDNN, ms	0.21	0.007	0.15	0.464
CV	0,22	0.005	0.11	0.609
RMSSD, ms	0.23	0.004	0.20	0.336
PNN50	0.24	0.002	0.06	0.791
HF, ms^2	0.22	0.005	-0.01	0.978
LF, ms^2	0.17	0.030	0.06	0.790
HF, %	0.18	0.022	-0.07	0.752
LF, %	-0.06	0.473	-0.09	0.671
S, %	-0.08	0.317	-0.41	0.039

HR: heart rate; SDNN: standard deviation of the NN interval (the time elapsing between two consecutive R waves in the electrocardiogram with normal sinus rhythm); CV: coefficient of variation; RMSSD, square root of the mean squared differences of successive NN intervals; PNN50: proportion derived by dividing NN50: the number of interval differences of successive NN intervals greater than 50 ms, by the total number of NN intervals; HF: high frequency band in absolute values (ms^2); LF: low frequency band in absolute values (ms^2); HF%: high frequency band in percentage of total spectral power; LF%: low frequency band in percentage of total spectral power; S: Index S of synchronization between the 0.1-Hz rhythms

i) HR and S index correlated with all sex hormones (estradiol[p], FSH[n], testosterone[p], and DHEAS[n]), where superscripts p and n denote a positive and negative correlation, respectively

ii) RMSSD, PNN50, HF, and HF% correlated with FSH[p], testosterone[n], and DHEAS[p]

iii) SDNN, CV, LF, and LF% showed no correlation with any sex hormones

In premenopausal women, only testosterone exhibited a weak correlation with SDNN, CV, PNN50, RMSSD, HF, and HF% (Spearman R ranged from 0.16 to 0.20, p<0.05). In postmenopausal women, the correlations were not found.

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After the exclusion of CVD patients, the correlation analysis gave the following results. In women without CVD, S index still correlated with all sex hormones (Spearman R ranged from 0.20 to 0.25, p<0.05), while HF correlated only with FSH and DHEAS (r=0.18, p=0.039 and r=0.21, p=0.016, respectively). Other indices showed no correlation with sex hormones. Age had no effect on the relationship between cardiovascular autonomic indices and sex hormones in the women.

Hot flashes and cardiovascular autonomic indices

We studied the relationships between hot flashes (binary parameter yes/no) and several cardiovascular autonomic indices in pre- and postmenopausal women using discriminant models. The following indices were included in the models: HR, SDNN, LF%, HF%, and S index. We also included age and the main predictors in the analysis. Patients with CVD were excluded from consideration to remove the uncontrolled effects of CVD on autonomic control.

We did not find any significant relationships between autonomic indices and the presence or absence of hot flashes. In premenopausal women, the constructed discriminant model (*Wilks' lambda* = 0.78 and *approximate* F (7.62)=2.56, p=0.022) showed lower predictive power than the model presented in Table 3. The percent of correctly classified cases using this model was 36.4% for women with hot flashes and 88.1% for women without hot flashes. The main predictor of hot flashes was also FSH.

In postmenopausal women, the constructed discriminant model had *Wilks' lambda*=0.62 and *approximate* F (7.47)=4.19, p=0.001. This model was also worse than the model presented in Table 3. In particular, the percent of correctly classified cases using this model was 68.8% and 73.9% for women with hot flashes and without them, respectively. The main predictor of hot flashes was estradiol.

Discussion

In our study, we found a significant difference in sex hormones between women with surgical and natural menopause. The obtained results are consistent with results reported by other authors (30, 31). Note that all women with surgical menopause included in our study were younger than 60 years. It is known that DHEAS level decreases with age (30). It is also known that smoking has an influence on steroid hormone concentrations (32). However, we did not find such an influence in our study. The impact of sex hormones on CVD in women is discussable and attracts a lot of attention (33-36). According to our study, sex hormones and menopause time are related similarly with some autonomic indices. According to Chaudhuri et al. (37), postmenopausal women exhibit significantly decreased HRV in comparison with premenopausal women. Some other differences between these groups of women were reported in other studies (38). We did not find significant relationships between the characteristics of menopausal status and autonomic indices, which are also considered cardiovascular risk factors (2, 3). Low correlations are discussable and have no clinical importance. In our study, only HR was different in pre-

and postmenopausal women, including patients with CVD. This observation contradicts the increase of sympathetic tone after menopause (10), which results in the increase of HR. In women without CVD, some spectral HRV indices (LF and HF) were also different. However, CVD masks the relationship between autonomic control and menopause.

Note that arterial hypertension was more frequent in postmenopausal women in our study, which is consistent with other studies (39-40). In the postmenopausal period, the increase of BP is associated with autonomic disturbances in the CVS, in particular, with the increase of sympathetic tone (9). Diabetes mellitus was observed only in postmenopausal women. Other authors also reported a greater frequency of glucose metabolism disturbances after menopause (41).

Moodithaya et al. (42) have shown a decrease of power of HF and LF spectral bands in the HRV power spectrum in postmenopausal women in comparison with premenopausal women. Age was the important factor responsible for the differences in all ranges of the HRV spectrum between pre- and postmenopausal women.

Tezini et al. (43) suggested the absence of a relationship between autonomic control and ovarian hormone deprivation in rats with early and physiological menopause. These results seem to be a consequence of the aging process. We confirmed this fact in postmenopausal women. The low correlation between testosterone and some autonomic indices, shown by us in premenopausal women, is a debatable point. In postmenopausal women without prior HRT, oral estradiol therapy versus transdermal estradiol reduced HRV in the time domain (SDNN, RMSSD, and triangular index) (44). Hautamäki et al. (45) reported positive effects of estradiol-only therapy on cardiovascular control in flushing women. It was also shown that estrogen therapy has a weak attenuating effect on some nocturnal nonlinear measures of HRV (46). But, Fernandes et al. (47) did not find any effects of HRT on 24-hour HRV in postmenopausal women.

The difference in estrogen level between pre- and postmenopausal women contributed to the difference in relative values of HF and LF bands in the HRV spectrum (42). In our study, the power of HF and LF spectral bands of HRV was not significantly different in postmenopausal versus premenopausal women. However, in the analysis restricted to women without CVD, the index RMSSD and both the HF and LF bands were significantly higher in postmenopausal versus premenopausal women. The inclusion of women with CVD into the analysis led to the masking of the relationship between menopausal status and HF and LF. The results of our study may be limited by its cross-sectional design (see the Limitations section).

According to the results of cross-sectional study by Carranza-Lira et al. (48), vasomotor symptoms (hot flashes and sweats) correlate only after menopause. Da Fonseca et al. (49) reported that the age of menopause and BMI may influence the intensity of vasomotor symptoms. In our cross-sectional study, the main predictors of hot flashes were sex hormone levels (FSH and estradiol in pre- and postmenopausal women, respectively). Autonomic indices and BMI were not related with hot flashes in

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the women studied. Lantto et al. (44) obtained similar results. They showed for postmenopausal women without HRT that HRV parameters are similar in subjects with hot flashes and without them. According to Hautamäki et al. (50), hot flashes and HRT were not related to the changes in HRV.

The absence of clinically meaningful relationships between cardiovascular autonomic indices and vasomotor symptoms in menopause revealed in our study agree with some other results (5, 10, 11, 44, 50). It is evident that changes in levels of sex hormones in menopause are the main factor determining vasomotor symptoms. The observed relationships between a number of autonomic indices and the level of sex hormones and menopause time indirectly indicate that autonomic indices exert an influence on the appearance of menopause symptoms. Interrelations between autonomic indices and vasomotor symptoms in menopause need further investigation.

Also, we did not find any relationship between autonomic indices and BMI, which is consistent with Moodithaya et al. (42). However, Mouridsen et al. (51) reported that weight loss seems to improve HRV. A relationship between BMI and LF and HF band of the HRV spectrum was reported only in premenopausal women (18, 52). The decrease of HF and increase of LF may be associated with central adiposity in postmenopausal women (53). According to Robillard et al. (54), healthy women with a metabolically healthy but obese (MHO) phenotype had significantly lower resting HR and higher SDNN and LF than women with obesity as a risk factor.

In our cross-sectional study, we did not reveal a clinically important relationship between cardiovascular autonomic control and menopausal status (pre- and postmenopausal period, menopausal time, sex hormones, and hot flashes) in women. A significant difference between pre- and postmenopausal women was found in a number of autonomic indices (HR, LF, and HF). In the case of CVD, there was no difference in LF and HF between the subgroups of women studied. The observed weak correlations between autonomic indices and some other parameters (hot flashes, sex hormones, menopausal time, and obesity) have no clinical impact. FSH was found to be the main predictor of hot flashes in premenopausal women in our study, while estradiol and age were found to be the main predictors of hot flashes in postmenopausal women.

Personal dynamics of sex hormone levels during menopause were not studied. The cross-sectional design of the presented study had some limitations. We can not examine individual dynamic features of the relationship between cardiovascular autonomic control and fertile status (sex hormone levels, menopause time, etc.). An additional comparative study of cardiovascular autonomic control features in pre- and postmenopausal women must be carried out during a prospective trial.

The overlap in age between pre- and post-menopausal women was small, because it was difficult to adjust for age accurately. Therefore, it was difficult to determine the influence of age on menopausal status. The small number of women with surgical menopause was a limitation of our study for the corresponding subgroup.

We did not study the duration of sleep among women. Since patients with menopause often have sleep disturbances, which

can affect HRV indices, it is also a limitation of the present study. We did not assess lipids and diet in women. An influence of lipid metabolism and diet type on CVS autonomic control was shown in some studies (55). We did not identify women with the MHO phenotype among obesity subjects. The influence of BMI on autonomic indices needs further investigation.

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