# Interaction between cardiovascular autonomic control and sex hormones in perimenopausal women under menopausal hormone therapy

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***Objective*** **The aim of this study was to assess the dynamical interaction between the cardiovascular autonomic control and sex hormones in perimenopausal women under menopausal hormone therapy (MHT).**

***Patients and methods*** **Seventy women (age: 51.6 ± 2.1 years) were treated with MHT. Standard time and frequency domain measures of heart rate variability (HRV) and index *S* of synchronization between the slow oscillations in HRV and photoplethysmographic waveform variability were studied during a 6-week treatment with MHT. We assessed also the dynamics of the following sex hormones: estradiol, follicle-stimulating hormone, dehydroepiandrosterone sulfate, and testosterone.**

***Results*** **MHT increased estradiol and decreased follicle-stimulating hormone. Hot flashes and index *S* were significantly decreased under MHT ($P < 0.05$). Other autonomic indices were not significantly changed ($P > 0.05$). Changes of index *S* did not correlate with changes of sex hormones and hot flushes ($P > 0.05$).**

***Conclusion*** **The obtained results may indicate the independence of heart autonomic control (assessed by HRV measures) from women's hormonal status. However, any changes in sex hormones contribute to changes in the systemic control of circulation, which is assessed by index *S*.** *Cardiovasc Endocrinol Metab* **7:58–63** 

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**Keywords: autonomic control, heart rate variability, low-frequency oscillations, perimenopause, sex hormones, synchronization**

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## Introduction

Women are known to have lower total heart rate variability (HRV) and lower power of slow oscillations than men. These sex-related differences diminish with age, especially at the time of menopause, which may suggest a potential hormonal influence on the autonomic nervous system [1]. In our previous cross-sectional study [2], we did not find a clinically important relationship between the cardiovascular autonomic indices [standard indices of HRV and index *S* of synchronization between the low-frequency (LF) oscillations in HRV and photoplethysmographic waveform variability (PPGV)] and menopausal status assessed by the level of sex hormones, menopause time, and hot flashes in women. Low correlation between the index *S* and some sex hormones has been shown, which has no clinical importance [2]. However, individual dynamical features of the relationship between the cardiovascular autonomic control and indices of clinical status of perimenopausal women, for example, sex hormone levels, were not studied in Neufeld *et al.* [2]. It was the main limitation of this previous study [2].

Menopausal hormone therapy (MHT) is used as an effective approach for the treatment of menopausal disorders, owing to the reduction of circulating estrogen levels [3–5]. Some authors have recommended MHT for cardiovascular prevention in addition to treatment of menopausal disorders [3,5]. However, the recent meta-analysis performed by Yang *et al.* [6] has not supported this concept.

It is known that autonomic dysfunction is an important factor for the evaluation of risk of cardiovascular events in patients with cardiovascular diseases [7,8]. The relationship between MHT and cardiovascular autonomic control is poorly understood. The results of studies in this field are controversial [9–17].

The aim of the present study is to assess the dynamical interaction between the cardiovascular autonomic control and sex hormones in perimenopausal women under MHT.

## Patients and methods

### Patients

This study was approved by the Ethics Committee of the Saratov Research Institute of Cardiology in Saratov, Russia, and informed consent was obtained from all participants.

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Our study included 70 perimenopausal women aged 51.6 ± 2.1 years (mean ± SD), who needed MHT [18]. The women were using MHT to reduce menopause symptoms such as hot flashes, night sweats, irritability, mood swings, and depression. Cardiovascular, gynecological, and other clinical characteristics were accessed in all women. Only the patients aged between 46 and 55 years were enrolled in our study. Women with hypertension did not have prior treatment with β-blockers or calcium channel blockers during 7 days before the start of the study.

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

(1) rhythm other than sinus that could impede the analysis of HRV,
(2) endocrine pathology, excluding diabetes mellitus,
(3) valvular defect of the heart,
(4) chronic gastrointestinal diseases (hepatitis, gastric ulcer, duodenum disease, and cholecystitis), chronic diseases of kidneys, neurological or respiratory disorders, and other chronic diseases in the stage of exacerbation,
(5) contraindications to MHT,
(6) history of polycystic ovary syndrome,
(7) patient's refusal from MHT.

Anthropometric and clinical characteristics of studied women are presented in Table 1.

**Table 1 Anthropometric and clinical characteristics of women with menopausal hormone therapy ($n = 70$) before treatment**

| Parameters | Values |
|---|---|
| Age (years) | 51 (46–55) |
| Vasomotor symptoms | 100 |
| Hot flashes | 94.3 |
| Night sweats | 15.7 |
| Previous MHT | 14.3 |
| Height (m) | 1.68 (1.63–1.71) |
| Weight (kg) | 75 (65–90) |
| BMI (kg/m$^2$) | 27.3 (24.5–32.5) |
| SBP (mmHg) | 120 (110–135) |
| DBP (mmHg) | 80 (70–90) |
| CHD, angina pectoris | 0 |
| Previous myocardial infarction | 0 |
| Arterial hypertension | 48.6 |
| Previous stroke | 0 |
| Diabetes mellitus | 0 |
| Smoking | 2.9 |
| Estradiol (pmol/l) | 49.2 (36.7–136.0) |
| FSH (IU/l) | 53.5 (33.1–75.1) |
| Testosterone (nmol/l) | 2.1 (0.9–3.1) |
| DHEAS (nmol/l) | 3.1 (2.4–5.6) |
| HR (beats/min) | 75.0 (68.8–81.7) |
| SDNN | 52.6 (25.7–86.5) |
| CV (%) | 5.7 (3.3–6.8) |
| RMSSD | 43.8 (18.3–69.1) |
| PNN50 | 6.4 (0.9–9.5) |
| TP (ms$^2$) | 592.2 (241.2–8146.1) |
| HF (%) | 30.7 (15.4–51.0) |
| LF (%) | 27.7 (17.7–35.8) |
| S (%) | 39.6 (31.5–46.5) |

Continuous variables are presented as median (interquartile range). Categorical data are presented as percentages.
CHD, coronary heart disease; CV, coefficient of variation; DBP, diastolic blood pressure; DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; HF (%), high-frequency band in percentage of total spectral power; HR, heart rate; LF (%), low-frequency band in percentage of total spectral power; MHT, menopausal hormone therapy; 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; RMSSD, square root of the mean squared differences of successive NN intervals; *S*, index *S* of synchronization between the 0.1-Hz rhythms; SBP, systolic blood pressure; SDNN, SD of the NN interval (the time elapsing between two consecutive R waves in the ECG with normal sinus rhythm); TP, total power of heart rate variability spectrum (ms$^2$).

### Design of study

This is a nonrandomized study with no placebo control group.

Seventy women were treated with MHT. As a drug for MHT, we used 17-β-estradiol and dydrogesterone (Femoston, 17-β-estradiol/continuously, and dydrogesterone/sequentially) one time per day with one tablet at 8:00–8:30 a.m. During this study, hypertensive women received treatment only with diuretics. During this study, hypertensive women received treatment only with diuretics.

To examine the cardiovascular autonomic control, we simultaneously recorded the signals of ECG and photoplethysmogram (PPG). The level of the following sex hormones was assessed: estradiol, follicle-stimulating hormone (FSH), dehydroepiandrosterone sulfate, and testosterone. The ECG and PPG signals and sex hormones were analyzed at the following checkpoints of our study:

(1) before the start of the treatment (stage A),
(2) after 3-week treatment with MHT (stage B),
(3) after 6-week treatment with MHT (stage C).

### Signal recording

To examine the cardiovascular autonomic control, we carried out HRV analysis and estimated a degree of synchronization between the LF oscillations in HRV and PPGV. PPG signal measured on the middle finger of the patient's hand and ECG were simultaneously recorded at rest. Both signals were recorded within 10 min in supine position.

All patients were investigated in the afternoon fasting under spontaneous breathing. The ECG and PPG 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 the 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 heart rate and PPG signals simultaneously

recorded within 10 min. We evaluated the following time domain HRV parameters: mean heart rate, SD of the NN interval, coefficient of variation, square root of the mean squared differences of successive NN intervals, 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 [7].

Total power (0–0.5 Hz) and power of high-frequency (HF; 0.15–0.4 Hz) and LF (0.04–0.15 Hz) bands of the HRV spectrum were analyzed [7]. Power of LF and HF bands was presented in percentages of total power (LF% and HF%). LF/HF ratio was also calculated [7].

To estimate the synchronization between the LF oscillations in HRV and PPGV, we used the method proposed by us recently [19]. Index $S$ defines the relative time of synchronization between the considered slow oscillations.

### Statistical analysis

Continuous variables are reported as medians with interquartile ranges (lower and upper quartiles). Categorical data are presented as frequencies and percentages. The obtained estimations were considered statistically significant, if $P$ was less than 0.05. For a statistical analysis, the software package Statistica 6.1 (StatSoft Inc., Tulsa, Oklahoma, USA) was used.

We applied the Shapiro–Wilk test to check whether the data are approximately normally distributed. As these data occur to be non-normal, their further analysis was carried out using nonparametric 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. Paired relationships between the continuous variables were assessed using Spearman's correlation coefficients (0.68–1.0 is high correlation, 0.36–0.67 is moderate correlation, and $\leq 0.35$ is low correlation [20]). Multiple regression analysis with sigma-restricted parameterization was used to study the multivariate effects for continuous and categorical variables.

## Results

MHT increased estradiol and decreased FSH (Table 2). The dynamics of testosterone and dehydroepiandrosterone sulfate did not have a clear trend (increase or decrease) under treatment that hampers its interpretation (Table 2). The frequency of hot flashes was significantly decreased under the 6-week treatment to 22.9% ($P < 0.001$ for pairs 'initial state vs. state after treatment'). We found a statistically significant decrease of index $S$ during MHT (Table 3). Other autonomic indices were not significantly changed under treatment (Table 3).

Correlation analysis was used to study the association between the cardiovascular autonomic indices, sex hormones, and hot flushes during MHT. We found no correlation between the hot flushes and all studied autonomic indices ($P > 0.1$). Even the index $S$, which appreciably varied during MHT, did not correlate with hot flushes (Spearman's $R = 0.06$, $P = 0.680$). Index $S$ was associated only with estradiol and FSH (Fig. 1). Other autonomic indices had no significant pair correlation with the level of sex hormones ($P > 0.05$).

We studied the details of multiple interactions between the index $S$ and sex hormones in stages of our study. The best multiple regression model with index $S$ as the dependent variable and all sex hormones as predictor variables has $R^2 = 0.24$, $P = 0.102$, which is not statistically significant. The multiple analysis has shown that testosterone is a predictor variable that is most associated with index $S$. The standardized ($\beta$) regression coefficient of testosterone is 0.32.

## Discussion

We found no significant dynamics of most cardiac autonomic indices under MHT, except the synchronization of LF oscillations in HRV and PPGV estimated by index $S$. MHT decreased this synchronization, which is a marker of the status of systemic autonomic regulation in cardiovascular system. Index $S$ characterized the degree of synchronization between the slow processes in baroreflector regulation of blood pressure (by total vascular conductance) and chronotropic regulation of the heart. We found no other studies on this synchronization in women under MHT.

Our results on time and frequency domain measures of HRV are consistent with the study by Hautamäki *et al.* [21]. These authors have shown that MHT do not

**Table 2 Level of sex hormones in studied perimenopausal women ($n = 70$) before the treatment (A), after 3-week treatment (B), and after 6-week treatment (C)**

| Stages | Estradiol (pmol/l) | FSH (IU/l) | Testosterone (nmol/l) | DHEAS (nmol/l) |
|---|---|---|---|---|
| A | 49.2 (36.7–136.0) | 53.5 (33.1–75.1) | 2.1 (0.9–3.1) | 3.1 (2.4–5.6) |
| B | 171.3 (116.0–284.2) | 31.0 (15.0–45.1) | 2.8 (2.1–3.8) | 4.5 (3.5–5.3) |
| | **$P^A < 0.001$** | **$P^A < 0.001$** | **$P^A = 0.029$** | $P^A = 0.427$ |
| C | 303.5 (221.5–431.0) | 13.4 (10.6–23.5) | 2.2 (2.0–2.9) | 3.8 (3.2–4.4) |
| | **$P^A < 0.001$, $P^B < 0.001$** | **$P^A < 0.001$, $P^B < 0.001$** | $P^A = 0.387$, $P^B = 0.146$ | $P^A = 0.412$, **$P^B = 0.005$** |

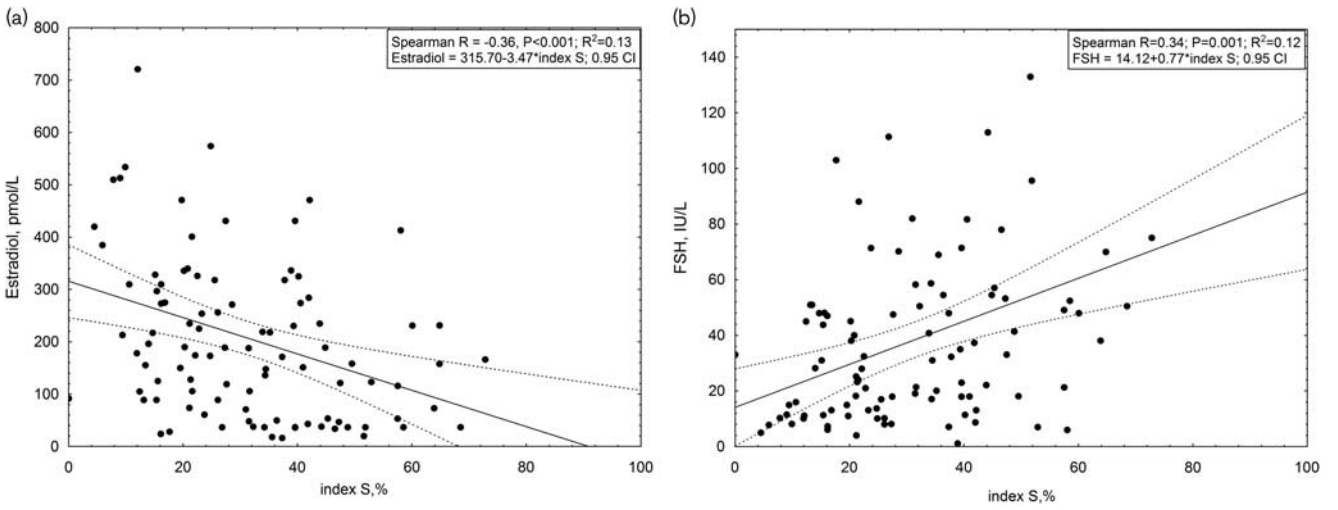
Bold values are statistically significant.
Data are presented as median (interquartile range).
DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; $P^A$ is $P$ level of Wilcoxon's test for the difference from the stage A; $P^B$ is $P$ level of Wilcoxon's test for the difference from the stage B.

**Table 3 Level of cardiovascular autonomic indices in the studied perimenopausal women ($n = 70$) before the treatment (A), after 3-week treatment (B), and after 6-week treatment (C)**

| Parameters | Stage A | Stage B | Stage C |
|---|---|---|---|
| HR (beats/min) | 75.0 (68.8–81.7) | 76.0 (66.0–86.5)<br>$P^A = 0.512$ | 79.0 (67.9–89.4)<br>$P^A = 0.374$, $P^B = 0.569$ |
| SDNN (ms) | 52.6 (25.7–86.5) | 45.1 (30.9–78.3)<br>$P^A = 0.451$ | 42.6 (34.2–63.9)<br>$P^A = 0.339$, $P^B = 0.732$ |
| CV (%) | 5.7 (3.3–6.8) | 5.4 (4.1–7.8)<br>$P^A = 0.461$ | 5.9 (4.2–6.5)<br>$P^A = 0.524$, $P^B = 0.569$ |
| RMSSD (ms) | 43.8 (18.3–69.1) | 39.8 (24.5–74.7)<br>$P^A = 0.694$ | 33.5 (21.7–68.9)<br>$P^A = 0.425$, $P^B = 0.785$ |
| PNN50 | 6.4 (0.9–9.5) | 10.1 (2.1–19.4)<br>$P^A = 0.612$ | 11.5 (2.1–24.3)<br>$P^A = 0.699$, $P^B = 0.219$ |
| TP ($ms^2$) | 592.2 (241.2–8146.1) | 849.2 (274.4–1771.8)<br>$P^A = 0.706$ | 823.9 (372.6–1243.9)<br>$P^A = 0.227$, $P^B = 0.246$ |
| HF (%) | 30.7 (15.4–51.0) | 26.6 (19.1–43.6)<br>$P^A = 0.623$ | 31.2 (18.4–48.1)<br>$P^A = 0.855$, $P^B = 0.399$ |
| LF (%) | 27.7 (17.7–35.8) | 29.4 (26.3–39.5)<br>$P^A = 0.534$ | 27.0 (18.9–37.3)<br>$P^A = 0.946$, $P^B = 0.202$ |
| LF/HF | 1.03 (0.48–2.40) | 1.03 (0.58–1.68)<br>$P^A = 0.694$ | 0.88 (0.47–2.25)<br>$P^A = 0.699$, $P^B = 0.554$ |
| *S* (%) | 39.6 (31.5–46.5) | 25.5 (15.6–41.9)<br>**$P^A = 0.027$** | 21.0 (14.9–26.8)<br>**$P^A < 0.001$, $P^B = 0.002$** |

Bold values are statistically significant.
Data are presented as median (interquartile range).
CV, coefficient of variation; HF (%), high-frequency band in percentage of total spectral power; HR, heart rate; LF (%), low-frequency band in percentage of total spectral power; $P^A$ is *P* level of Wilcoxon's test for the difference from the stage A; $P^B$ is *P* level of Wilcoxon's test for the difference from the stage B; 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; *S*, index *S* of synchronization between the low-frequency oscillations in heart rate variability; TP, total power of heart rate variability spectrum.

**Fig. 1**




Scatterplot of index *S* against estradiol (a) and follicle-stimulating hormone (FSH) (b). CI, confidence interval.

significantly modify the HRV responses in women with or without hot flushes. In our study, the decrease of hot flushes was not associated with dynamics of studied cardiovascular autonomic measures. The absence or very low power of relationship between MHT and cardiovascular autonomic control was previously reported also by some authors [22–25].

Our results are not consistent with some studies. For example, Perseguini *et al.* [13] reported an increase of cardiac sympathetic modulation under MHT, accessed by LF and LF/HF. In the study by Rosa Brito-Zurita *et al.* [14], estrogen increased the parasympathetic tone in cardiovascular control that contradicts the results of Perseguini and colleagues. Magri *et al.* [26] reported that MHT seems to play a positive role in the autonomic modulation of cardiac function through a shift of LF/HF ratio values toward those in young patients.

Yang *et al.* [27] reported a decrease of LF% in perimenopausal women treated with estrogens, but not in women treated with combined estrogen–progestin substitution

therapy. In this last group of women, the combined estrogen–progestin substitution therapy had no effect on HRV. However, Farag *et al*. [11] obtained the contradictory results. In our study, all women were treated with estrogen–progestin drug (17-β-estradiol and dydrogesterone).

## Conclusion

In our study, we did not reveal a clinically important relationship between the changes of time and frequency domain measures of HRV and dynamics of sex hormones under MHT. Synchronization between the LF oscillations in HRV and PPGV was significantly decreased under treatment. However, this decrease of synchronization did not correlate with the dynamics of sex hormones profile and hot flushes.

In our opinion, these results may indicate the functional independence of heart autonomic control, assessed by HRV measures, from the regulatory system of women's hormonal status. At the same time, any changes in women's hormonal status, for example, under MHT, contribute to the changes in the systemic regulation of blood circulation, assessed by the index of synchronization between the LF oscillations in HRV and PPGV. Clinical impact of the presented results needs to be clarified in future studies.

### Study limitations

This is a nonrandomized study with no placebo control group, which is a weakness of the study design.

Because of the small number of women in the studied group, we have not investigated the impact of hypertension on the relationship between the cardiovascular autonomic control and sex hormones under MHT.

We studied a mixed group of women in terms of mensis status. Part of the studied women have mensis, but they have been prescribed treatment with MHT because of the perimenopausal disorders. During women's stratification based on mensis, we found no significant impact of mensis on our statistical results. We believe that levels of sex hormones are a key factor in determining the menopausal status (mensis disorders, hot flushes, etc.) in women. Thus, we studied only the interaction between sex hormones profile and cardiovascular autonomic control in mixed group of perimenopausal women.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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