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Hemodynamic Allostasis of Pregnant Women against the Background of Preeclampsia

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We analyzed diurnal hemodynamic parameters (HR, systolic BP, and diastolic BP) recorded from two groups of edematous and preeclamptic pregnant women. The unidirectional character of changes in the control over the functional state of cardiovascular system was revealed except for the indices, which mark a pathological process: elevated diurnal BP in preeclampsia and diminished percentage of oscillation power in edematous patients. Uniformity of the regulatory changes in patients with and without arterial hypertension can be viewed as manifestation of allostasis developed by the cardiovascular system during pregnancy. In preeclampsia, the greater allostatic load was reflected by the changes in diurnal, daytime, and nighttime BP and in the circadian index calculated for HR, systolic BP, and diastolic BP. In edematous patients, elevation of allostatic load was indicated by the percentage of ultradian rhythms.

Key Words: *pregnancy; allostasis; preeclampsia; edemas in pregnancy; ultradian rhythms*

Development of the fetus during pregnancy is tightly coupled with the adaptive reactions of the cardiovascular system aimed at the formation and maintenance of hypervolemia via activation of the renin—angiotensin—aldosterone system (RAAS). Importantly, the pregnancy is accompanied by increasing resistance of maternal blood vessels to angiotensin II, which secures their stability under elevated volume of circulating blood [3]. However, insufficient invasion of the cytotrophoblast and incomplete gestational rearrangement of the spiral and radial arteries often lead to diminished uteroplacental blood flow fraught with the development of placental ischemia. In their turn, inadequate placentation and aggravating ischemia of the placental tissue can provoke the release of cytotoxic factors that induce endotheliosis in the microcirculatory bed not only in the uterus, but also in the target organs. Under these conditions, the cells and tissues undergo structural and functional rearrangements determined by cytoplasm swelling and deposition of fibrin around the basal membrane, which affect diffusion of blood gases in tissues and can provoke hypoxia [5]. These shifts cannot be considered as homeostatic, because they are provoked by gestation and should disappear after its termination. Thus, they should be rather considered as allostasis [4], which means "achieving stability through changes" [6].

The disturbances in the mechanisms, which control the cardiovascular system, can provoke not only an abnormal adaptation of the female organism during pregnancy aggravated by various pathologies [1,7] such as preeclampsia, but also the development of arterial hypertension (AH) at the delayed period. Actually, the women who suffer from preeclampsia during the pregnancy demonstrate a pronouncedly increased postpartum BP and body weight index [4]. Partially, it can be explained by enhanced sensitivity to angiotensin II during preeclamptic state [3]. The development of preeclampsia as a pathological variant of pregnancy course is paralleled by changes in activity of RAAS proteins; it is believed that polymorphisms of the genes coding angiotensinogen (ATG), angiotensin-converting enzyme (ACE), and angiotensin II type 1 receptor (AGT1R) are related to the development of preeclampsia [8]. These changes can be responsible for possible development of AH at the background

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preeclampsia, which can be maintained even after the pregnancy.

Logically, it seems important to comparatively study the peculiarities of the daily monitored profile of BP in pregnant patients with preeclampsia and in non-preeclamptic edematous pregnant women. According to modern views, the edema in pregnancy not accompanied by preeclampsia is not considered as pathology because their combined manifestation is observed in 60% cases. This comparison can decide whether AH in preeclamptic cases develop via peculiar regulatory mechanisms or it is formed within the framework of the allostatic load on cardiovascular system caused by the pregnancy.

MATERIALS AND METHODS

The examined pregnant women were subdivided into 2 experimental groups. The group 1 (N=30) consisted of the preeclampsia patients at 30-39 week of gestation and aging 23-37 years. The inclusion criteria in this group corresponded to the treatment protocol (clinical recommendations) "Hypertensive Disorders in Pregnancy, Delivery, and Postpartum Period. Preeclampsia. Eclampsia, 2016" issued by Ministry of Health of the Russian Federation in compliance to Federal Law Article 76, No. 323-FZ (November 21, 2011) "On Basics of Health Protection of the Citizens in the Russian Federation". Group 1 patients were hospitalized for elevated BP>140/90 mm Hg. The peculiarities of their anamnesis included: *1*) excessive weight gain (73% cases), *2*) toxemia and risk for preterm labor (33% cases), *3*) placental insufficiency (37% cases), and 4) proteinuria in single-voided urine specimen (50% cases).

Group 2 (n=30) comprised patients aging 24-34 years at gestation week 27-40, who had peripheral edemas not accompanied by AH and proteinuria. These patients were hospitalized in relation to rapid body weight gain (>500 g per week). In addition, all of them demonstrated maternal hydrops syndrome. The total body gain surpassed the norm in 62% cases, whereas in 21, 18, and 32% patients, there were, respectively, the risks of preterm deliveries, toxicosis, and placental insufficiency. However, these patients had no proteinuria.

The patients of both groups received treatment permitted at these types of pathology in gravidae. The exclusion criteria for both groups were AH prior to pregnancy and secondary forms of AH.

TABLE 1. Parameters of 24-h Profile of BP and HR in Preeclampsia and Edemas in Pregnancy Assessed with Linear Analysis of Rhythm (m±SEM)

Parameter	Healthy women	Edematous gravidae	Preeclampsia
Diurnal			
sBP	115.00±1.29	111.06±1.58	123.86±1.47*+
dBP	72.20±1.75	67.56±0.96*	75.63±1.25+
HR	72.08±1.01	81.67±1.64*	82.73±1.42*
Daytime			
sBP	120.75±1.73	114.91±1.65	126.86±1.53+
dBP	75.86±2.02	70.76±1.01*	78.11±1.31+
HR	74.61±1.39	84.86±1.59*	85.25±1.37*
Nighttime			
sBP	95.28±2.19	103.10±1.79	117.66±1.89*+
dBP	57.85±1.03	60.94±1.23	70.51±1.48*+
HR	62.29±3.47	75.07±1.94*	77.53±1.73*
CI			
sBP	1.27±0.04 (96%)	1.06±0.01(80%)*	1.02±0.02 (78%)*
dBP	1.31±0.03 (100%)	1.12±0.02 (85%)*	1.06±0.02 (81%)*+
HR	1.22±0.08 (93%)	1.07±0.02 (82%)*	1.05±0.02 (80%)*
SPBP			
sBP	0.62	0.61	0.61
dBP	0.63	0.62	0.62
HR	0.61	0.59	0.59

Note. Here and in Table 2: $p \leq 0.05$ in comparison with *control and +edematous gravidae.

The control group (N=7) consisted of healthy non-pregnant women aging 16-57 years. All participants gave informed consent for participation in the study.

In all cases, BP was daily monitored with a TM-2430 (A&D) blood pressure monitor. BP and HR were recorded every 30 min during day and night.

The data were processed with EZ Doctor and Chronos-Fit software using linear and non-linear analyses of rhythm [9]. The latter is a partial Fourier analysis combined with stepwise regression.

The linear analysis was employed to calculate the mean systolic and diastolic BP (sBP and dBP, respectively) and HR for daytime, night, and the whole day. For the examined parameter, the non-linear rhythm analysis yielded the mesor (the mean value during the period), magnitude (maximal deviation from the mesor), peak-to-peak value during the period, oscillation power (%rhythm, *i.e.*, the percentage of daily oscillating parameter, corresponding to its oscillating part).

The following parameters were calculated: structural point of BP (SPBP) defined as dBP/sBP ratio and the circadian index (CI) obtained as the ratio of the average value of examined parameter during the daytime to average nighttime value of this parameter.

The data were analyzed statistically using Statistica 6.0 (StatSoft) software, Student's *t* test, and one-tailed Fisher angular conversion φ test (applied for the fractions and percentages) at $p \leq 0.05$. The results are summarized as m±SEM. The relationships between sBP and dBP, sBP and HR, as well as dBP and HR were assessed with the Pearson's correlation coefficient *r*.

RESULTS

Comparative analysis of hemodynamic indices (sBP, dBP, and HR) performed with linear and linear and non-linear analyses (Tables 1, 2) revealed the significant differences in some parameters, which mark the pathological process in each group. The diurnal, daytime, and nighttime levels of sBP and dBP were significantly higher than the respective parameters in the edematous group. The edematous women demonstrated significant elevation of HR %rhythm due to its ultradian component. In hemodynamic allostasis in pregnancy, only 9 indices differed significantly between the examined groups. These indices characterized peculiarities of the pathological process developing in pregnant women: 2 indices related to edema and 7 indices were associated with AH. The similarly changes in the conditions of circulation control can be reported by SPBP in both experimental groups (Table 1), which probably reflects the state of endotheliosis typical in pregnancy [5]. The absence of any significant differences of this parameter between 3 examined groups indicates that the degree of perfusion changes were not critical for circulation control.

In experimental groups, %rhythm and peak-to-peak value for sBP and dBP were significantly smaller than the control levels indicating a marked disturbance of the cardiovascular system chronostructure and degradation of its adaptive potencies. At this, the described changes were unidirectional as attested by the absence of significant differences between both experimental groups in magnitude, power, and peak-to-peak value of the rhythm. Even the peak-to-peak

TABLE 2. Parameters of 24-h Profile of BP and HR during Preeclampsia and Edemas in Pregnancy Assessed with Non-Linear Analysis of Rhythm (m±SEM)

Parameter		Healthy controls	Edematous gravidae	Preeclamptic gravidae
Mesor	sBP	112.00±1.00	110.97±1.58	123.84±1.47*+
	dBP	69.88±1.52	67.51±0.97	75.58±1.25*+
	HR	70.69±1.05	81.60±1.64*	82.73±1.42*
Magnitude	sBP	18.53±1.60	14.08±1.44	13.44±1.05*
	dBP	15.15±0.95	10.78±1.13	9.65±0.77*
	HR	14.21±0.9	14.18±2.53	11.50±1.14
Oscillation power (%rhythm)	sBP	61.26±3.96	33.59±3.20*	33.23±3.05*
	dBP	50.07±2.77	27.90±2.17*	27.15±2.35*
	HR	55.65±5.83	41.12±4.15+	35.57±3.31*
Peak-to-peak value	sBP	44.77±4.34	29.43±2.73*	27.51±2.04*
	dBP	34.19±2.20	22.85±2.00*	19.89±1.59*
	HR	31.87±2.61	23.00±1.96*	22.6±1.97*

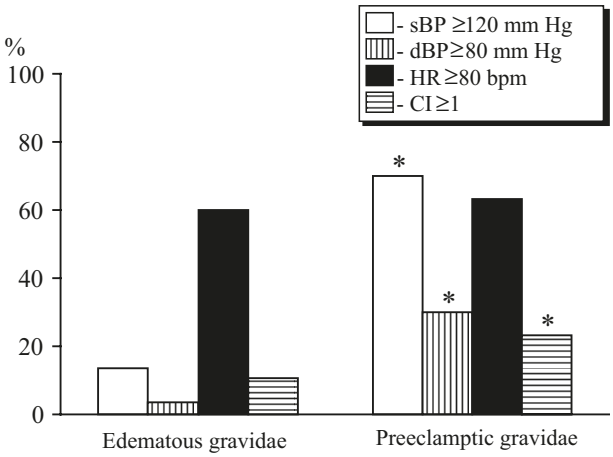

Fig. 1. Percent of patients in each experimental group with pronounced diurnal changes of hemodynamic parameters. *$p \leq 0.05$ in comparison with edematous group. CI≤1 was assessed simultaneously by 3 parameters (sBP, dBP, and HR).

values of hemodynamic indices in both experimental groups did not differ significantly attesting to similar adaptive potencies of the cardiovascular system.

The data (Tables 1 and 2) confirmed the important observation that the control of central hemodynamics in pregnancy is exerted not only within the framework of homeostasis but additionally, it is affected by the developing allostasis. To test this hypothesis, we compared the experimental and control hemodynamic indices. Actually, the hemodynamics of preeclamptic or edematous patients differed from the control in 10 or 9 of 12 indices, respectively (Table 1). The nonlinear analysis showed that the rhythm of preeclamptic or edematous patients differed from the control in 9 or 8 of 12 indices, respectively (Table 2).

Analysis of the relationships between hemodynamic parameters in both experimental groups revealed unidirectional correlations in these groups (Table 3), which also corroborates the hypothesis on allostatic mechanism controlling hemodynamics during pregnancy in edematous and preeclamptic gravidae. Moreover, this analysis showed pronounced weakening (in preeclamptic group) or complete elimination (in edematous group) of correlation between BP and HR, which is characteristic for the norm [2]. Probably, this fact attests to existence of different control influences, which shape the dynamic changes of BP and HR during pregnancy.

It seems reasonable to hypothesize that dynamics of BP changes depends on deviation of activity of RAAS proteins, while the peculiarities of HR reflect the level of adaptive sympathicotonia indicated by elevation of HR mesor in both groups in comparison with mean value and percent of patients without the nighttime drop of HR (30% in the preeclamptic group and 13.8% in the edematous group). During the development of edemas, 67% of the diurnal HR rhythm regulation was determined by the ultradian rhythm (6-4 h) related predominantly to diurnal oscillations of electrolytes [1], and it was accompanied by significant elevation of HR rhythm power assessed by non-linear analysis (Fig. 1).

The differences between edematous and preeclamptic groups cannot be revealed by analysis of the means, but are detected by assessing the proportion of patients with changed levels of diurnal BP and HR regulation (Fig. 1). In the preeclampsia group, the proportion of women with BP>120/80 mm Hg was higher than in the edematous group; in addition, the preeclamptic gravidae more frequently demonstrated a decrease in CI assessed by 3 examined parameters, which indicated disturbances in the control of central hemodynamics especially at the nighttime. In the preeclamptic group, the nighttime drops of sBP, dBP, and HR were observed in only 70, 66.6, and 70% cases, respectively, whereas in the edematous group the corresponding drops of these parameters were documented in 86% cases. These data indicate a greater allostatic load in preeclamptic gravidae in comparison with the edematous patients. By this view, the adaptive variations of diurnal hemodynamic are less disturbed in

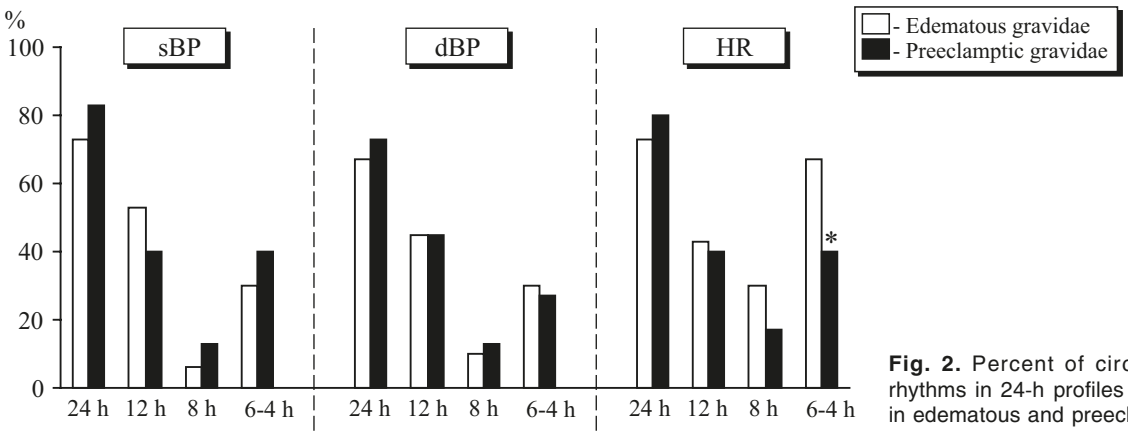

Fig. 2. Percent of circadian and ultradian rhythms in 24-h profiles of sBP, dBP, and HR in edematous and preeclamptic gravidae.

TABLE 3. Pearson's Correlation Coefficients between Hemodynamic Parameters of Edematous and Preeclamptic Gravidae

Pairs of variables	Edematous gravidae	Preeclamptic gravidae
Diurnal		
sBP—dBP	r=0.79	r=0.73
sBP—HR	r=–0.04	r=–0.22
dBP—HR	r=0.04	r=–0.14
Daytime		
sBP—dBP	r=0.76	r=0.74
sBP—HR	r=0.02	r=–0.18
dBP—HR	r=0.07	r=–0.14
Nighttime		
sBP—dBP	r=0.85	r=0.76
sBP—HR	r=–0.08	r=–0.09
dBP—HR	r=0.08	r=–0.03

edematous pregnant women then in the preeclamptic ones. Thus, the mean diurnal hemodynamic indices and chronostructural parameters of BP and HR reflect the allostatic load, which develops during pregnancy. Here, the exceptions are the indices marking a pathologic process (AH in preeclamptic gravidae, Tables 1, 2) and the percent of ultradian rhythms in edematous pregnant women (Fig. 2). Higher percent of patients with altered nighttime BP profile in the preeclampsia group (Fig. 1) attested to higher allostatic load associated with this pathology.

Examination of basic and integral parameters describing the diurnal dynamics of BP and HR made it possible to establish uniformity in the changes of the basic mean parameters and of the indices, which characterize the state of hemodynamics and its chronostructure in both groups of pregnant patients except for the markers of pathological process. Similar unidirectionality of the changes in preeclamptic and edematous cases was revealed by analysis of SPBP and CI. The character of correlations between the hemodynamic parameters was also equally changed in both experimental groups, where the normal correlations between HR and sBP as well as between HR and dBP were lost. Therefore, the revealed changes in diurnal hemodynamics were interpreted as the consequence of allostatic load on hemodynamics caused by pregnancy.

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