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Staging of Hemodynamic Parameters during Development of Experimental Arterial Hypertension in Rabbits

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The study analyzed changes in parameters of the central and intracardiac hemodynamics during the development of experimental arterial hypertension, which were assessed as the adaptive in nature. The development of hypertension demonstrated staging of the adaptive processes. The development of the adaptive responses was characterized by changes in the magnitude and probabilistic distribution of the hemodynamic parameters.

Key Words: *cardiovascular system; arterial hypertension; adaptation; entropy*

Various models of experimental arterial hypertension in animals open the way to analyze the mechanisms of its development. The model based on aorta narrowing above the origin of the renal arteries provoking renal ischemia is a tool to examine the effect of the renin–angiotensin–aldosterone system on the development of arterial hypertension.

Our aim was to examine staging of this process by analyzing changes in systemic and intraventricular pressure (IVP) by methods of descriptive statistic, correlation, and entropic analyses.

MATERIALS AND METHODS

Experiments were performed on 25 male Chinchilla rabbits weighing 2.5-3.5 kg. The following hemodynamic parameters of the cardiovascular system were monitored: systolic (SBP) and diastolic (DBP) blood pressure, operating IVP in the left (OIVPl) and right (OIVPr) ventricles under conditions of experimental vasorenal arterial hypertension. The animals were randomized into 5 groups (5 rabbits per group). The control group comprised intact rabbits. In all experimental groups, vasorenal arterial hypertension was modeled by surgical narrowing of the abdominal aorta by $^1/_3$ of its initial diameter above the origins of the renal arteries under general anesthesia. On postoperation weeks 1, 2, 4, and 6, the following parameters were measured with a MIKARD hardware-software system: OIVPl, OIVPr, SBP, and DBP.

For evaluation and comparison of variability of the cardiovascular hemodynamic parameters, they were processed by descriptive statistical analysis [4]. For all parameters obtained in the control and on postoperation weeks 1, 2, 4, and 6, the mean and SEM ($M\pm m$) as well as the variation coefficients V were calculated. The increment rate values (relative increments in percents per week) were assessed as BP (IVP) values on postoperation week 1 relatively to the corresponding control values, and as the same parameters on week 2 relatively to the corresponding data on week 1, *etc*. The state of the cardiovascular system was assessed by autocorrelation analysis [5]. Apart from cardiovascular parameters, we analyzed their probabilistic distributions reflected by coefficient of skewness *As*, excess coefficient *Ex* [4], and regulatory coefficient *R*

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TABLE 1. Dynamics of Hemodynamic Parameters in Control and during Experimental Arterial Hypertension in Rabbits (*M*±*m*)

Parameter	Control	Postoperation period			
		week 1	week 2	week 4	week 6
SBP	139.4±1.1	167.6±1.9	152.9±3.4	173.8±4.1	176.4±3.7
DBP	111.2±1.3	130.5±1.4	115.8±3.2	124.4±3.8	126.1±3.3
OIVPl	150.1±3.4	186.1±4.7	157.6±5.7	185.1±5.3	182.8±4.2
OIVPr	35.2±1.4	25.1±0.9	24.8±1.1	30.3±2.9	38.6±2.5

[1,7] determining the character of the control over the probabilistic variety of the parameters. It is a common view that $0 \le R \le 0.1$, $0.1 < R \le 0.3$, and $0.3 < R \le 1.0$ correspond to stochastic, quasi-deterministic, and deterministic modes of control [1,7].

RESULTS

Tables 1 and 2 show the dynamics of the mean values of hemodynamic parameters at different terms of the experiment.

The maximal adaptive response of the system characterized by elevation of all examined parameters was observed at the early period (postoperation week 1) when renal ischemia was the most severe. As the specific adaptive mechanisms became engaged, in particular, elevation of the aldosterone level [8] observed on postoperation week 2 due to the development of hypervolemia, systemic BP decreased. Further development of the adaptive response is underlain by up-regulation of the renin–angiotensin–aldosterone system resulting in remodeling of the heart and blood vessels accompanied by persistent elevation in BP [2,6,8]. Probably, the increase in the vascular tone in greater circulation promotes elevation of OIVPl on weeks 2 to 4, while in lesser circulation it increases OIVPr on weeks 2 to 6 (Tables 1 and 2).

The study showed staging in the development of this adaptive response to chronic renal ischemia (Table 3). Evolution of autocorrelation of the central and intracardiac hemodynamic parameters revealed differences in the status of the cardiovascular system during the examined period (Table 3). According to SBP, the qualitative changes in the work of this system occurred during transition from the control period to postoperation week 1, and from week 2 to week

TABLE 2. Increment Rates of Hemodynamic Parameters (%) in Control and during Experimental Arterial Hypertension

Parameter	Control–week 1	Week 1–week 2	Week 2–week 4	Week 4–week 6
SBP	20.2*	-8.8*	13.7*	1.5
DBP	17.4*	-11.3*	7.4*	1.4
OIVPl	24.4*	-15.6*	17.4*	-1.2
OIVPr	-28.6*	-1.3	22.1*	27.5*

Note. Significance of increment was *p<0.01.

TABLE 3. Autocorrelation of Hemodynamic Parameters (%) in Control and during Experimental Arterial Hypertension

Parameter	Control–week 1	Week 1–week 2	Week 2–week 4	Week 4–week 6
SBP	-0.668*	-0.075	0.704*	0.443*
DBP	0.068	0.516*	0.136	0.408*
OIVPl	-0.544*	0.619*	-0.258	0.391
OIVPr	0.587*	0.393	-0.578*	-0,479*

Note. Significance of the difference from zero was *p<0.05.

4. Evaluation of OIVPl autocorrelation revealed its dramatic change with sign inversion during transition from week 1 to week 2 culminated by disappearance of this correlation. At the same time, OIVPr changed its status during transition from the control period to postoperation week 1 as well as from week 2 to week 4, although this parameter retained the status during transition from week 4 to week 6.

Despite the revealed pronounced changes in autocorrelation of the examined central and intracardiac hemodynamic parameters, the dynamics of variation coefficients of these parameters (Table 4) revealed only insignificant changes in these coefficients for SBP and DBP on week 1 followed by their increase almost 2-fold on week 2, and then (weeks 4 and 6 the coefficients) remained elevated. For intracardiac pressure in the left and right ventricles, the changes in variation coefficients at various terms of experiment were far less pronounced, though the variation coefficient for the OIVPr significantly surpassed that for OIVPl on weeks 4 and 6 (Table 4), which corroborates the hypothesis of the leading role of the right subdivisions of the heart in adaptation [3].

The dynamics of *As* and *Ex* coefficients (Table 4), which assess skewness of probabilistic distribution, showed that the adaptive response of the cardiovascular system affected not only the hemodynamic parameters, but also their probabilistic distributions. Although *As* coefficients varied pronouncedly throughout the experiment, they did not significantly differ from zero in the control and at different terms postoperation (Table 4). In contrast, *Ex* coefficients (Table 4) significantly differed from zero on week 1 (for SBP and DBP) and on week 4 (for SBP, OIVPl, and OIVPr). The changes of *Ex* for SBP, OIVPl, and OIVPr on week 4 confirm the effects of the factors of specific adaptation on probabilistic profile of hemodynamic parameters, which reflects their control role. The number of significant differences of *Ex* from zero was the greatest also on week 4, when the structural and functional rearrangement of the system is probably terminating. This observation agrees with hypothesis that the cardiovascular system accomplished its adaptive response to the pathological factor. This is also seen from the dynamics of control coefficient *R* that affects the probabilistic variety for SBP (Table 4). Assessment of the mean value of *R* coefficient for the examined hemodynamic parameters at all the terms of the study shows that completion of transition of the system to a new hemodynamic state was accompanied by increasing the contribution of the stochastic component to the control of the system

TABLE 4. Descriptive Statistics and Entropy Analysis of Hemodynamic Parameters in Control and during Experimental Arterial Hypertension

Parameter		Control	Week 1	Week 2	Week 4	Week 6
Variation coefficients V	SBP	0.021**	0.029**	0.056**	0.060**	0.053**
	DBP	0.029**	0.028**	0.071**	0.078**	0.067**
	OIVPl	0.057**	0.065**	0.093**	0.073**	0.058**
	OIVPr	0.101**	0.093**	0.111**	0.241**	0.165**
Coefficients *As*	SBP	-0.415	0.175	-0.614	0.022	-0.200
	DBP	-0.123	-0.187	0.472	-0.305	0,096
	OIVPl	-0.107	-0.528	0.112	0.166	0.110
	OIVPr	-0.154	0.057	0.239	-0.075	-0.793
Coefficients *Ex*	SBP	-0.491	-1.509*	-0.673	-1.482*	-1.174
	DBP	-0.497	-1.428*	-0.587	-0.930	-0.903
	OIVPl	-0.202	-1,011	-0.563	-1.749*	-0.798
	OIVPr	0.251	-1.002	-0.891	-1.465*	-0.532
Coefficients *R*	SBP	0.069	0.220	0.248	0.064	0.043
	DBP	0.160	0.046	0.071	0.053	0.070
	OIVPl	0.106	0.063	0.188	0.069	0.036
	OIVPr	0.164	0.117	0.064	0.125	0.149
Mean $\bar{R}$		0.12	0.11	0.14	0.08	0.08

Note. Significance of the difference from zero was $^{**}p<0.01$ and $^{*}p<0.05$.

and by insignificant changes in mean $\overline{R}$ within the range of 0.08-0.14.

Thus, the study of the dynamics of experimental hypertension in rabbits revealed staging in this process related to transition from non-specific adaptation to the specific one, which was accompanied by a significant elevation of systemic BP and changes in the strength of the control over variation and the control coefficients. Normalization of coefficient R controling probabilistic variety of SBP by postoperation week 6 despite elevated systemic BP suggests that this hypertensive effect is not as an adaptive response of the cardiovascular system to ischemia rather than persistent pathologic process, which should be taken into consideration in the studies with modeling experimental arterial hypertension.

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