System Analysis of Changes in Cardiovascular Circulatory Dynamics in Experimental Diphtheria in Rabbit

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 148, No. 9, pp. 266-269, September, 2009
Original article submitted March 24, 2009

Trivariate correlation analysis of hemodynamic indices of the cardiovascular system in rabbits with diphtheria showed that adaptation of this system to direct action of diphtherin can be visualized by analysis of trivariate correlation tightness for indices of intraventricular pressure in the left and right ventricles and indices of systemic blood pressure. Using empirical production functions for systemic blood pressure indices we found that the contribution of intraventricular pressure in the left and right ventricles on blood pressure values is changed in diphtheria compared to the control. Basing on entropy analysis we established that the regimen of control over values of working intraventricular pressure in both left and right ventricles in diphtheria is changed from quasidetermined to stochastic.

Key Words: *diphtheria, adaptation, production function, entropy*

From a systemic point of view, the heart is a subsystem of the whole cardiovascular system [6]. Previous morphological studies of rabbit myocardium in diphtheria demonstrated progressive damage to both heart ventricles, damage to the right ventricle being less pronounced [9]. In this context it is interesting to investigate the mechanisms of cardiovascular adaptation to heart damage is diphtheria using methods of systemic analysis.

MATERIALS AND METHODS

Experiments were performed on 120 intact and 25 diphtheritic male Chinchilla rabbits weighing 2.6-3.5 kg. Experimental data were obtained at the Department of Pathological Physiology of Peoples' Friendship University of Russia on December 11-15, 1989, and on December 21-23, 1984. Diphtheritic intoxication was modeled by single intravenous administration of 0.3 minimum lethal dose (MLD) of native diphtherin per 1 kg body weight. Indices of cardiovascular circulatory dynamics, systolic and diastolic blood pressure (BP_s and BP_d) and working intraventricular pressure in the left and right ventricles ($LVIP_w$ and $RVIP_w$) were measured 1, 3 and 5 days after toxin injection. The data from the experiment carried out on December 21-23, 1984, was used as control.

To estimate the values and to compare the variability and distribution of these indices, descriptive statistical analysis was used [5]. The arithmetic means, coefficients of variation, skewness, and kurtosis were calculated. To reveal systemic associations between $LVIP_w$ (x) and $RVIP_w$ (y) values and BP_s (z) and BP_d (w) values, trivariate correlation analysis of correlation tightness was performed using overall coefficient of correlation r_{xyz} (r_{xyw}) [5]:

$$r_{xyz}=\frac{r^2_{xz}+r^2_{yz}-2r_{xy}r_{xz}r_{yz}}{1-r^2_{xy}}$$

$$r_{xyw}=\frac{r^2_{xw}+r^2_{yw}-2r_{xy}r_{xw}r_{yzw}}{1-r^2_{xy}}$$

where r_{xy}, r_{xz}, r_{yz}, r_{xw}, r_{yw} are pair coefficients of correlation between x and y, x and z, y and z, x and w, y and

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0007-4888/09/1483-0378

w. Overall coefficient of trivariate correlation always has a non-negative value and varies from 0 to 1: $0 \le r_{xyz}$ (r_{xyw})≤ 1. Tightness gradation was performed according to Harrington Verbal Numeric scale: 0.00-0.20 (very weak), 0.21-0.37 (weak), 0.38-0.64 (medium), 0.65-0.80 (strong), 0.81-1.00 (very strong). Significance of overall correlation coefficient r_{xyw} (r_{xyw}) was estimated using standard procedures.

To estimate the contributions of *x* ($LVIP_w$) and *y* ($RVIP_w$) into the formation of *z* and *w* values (BP_s and BP_d) we used trivariate regression analysis [2]. First we calculated *x* and *y* values ($LVIP_w$ and $RVIP_w$) and *z* and *w* values (BP_s and BP_d) in diphtheria and in control. Then on the basis of obtained values empirical production function for and *z* and *w* indices (BP_s and BP_d) were derived for two variables $\hat{z}=\hat{x}^{\alpha 1}/\hat{y}^{\alpha 2}$ and $\hat{w}=x^{\beta 1}/y^{\beta 2}$ [2] which describe the association between *x* ($LVIP_w$), *y* ($RVIP_w$), $\hat{z}$ (BP_s) and *w* (BP_d) indices. Coefficients of elasticity $\alpha 1$, $\alpha 2$ for the production function BP_s $z=x^{\alpha 1}/y^{\alpha 2}$ indicate that change in *x* value ($LVIP_w$) by 1% leads to change in *z* value (BPs) by α_1%, and change in *y* value ($RVIP_w$) by 1% leads to change in *z* value (BP_s) by α_2%. Similarly coefficients of elasticity β_1 and β_2 for the production function BPd $\hat{w}=x^{\beta 1}/y^{\beta 2}$ take into account the contribution of *x* ($LVIP_w$) and *y* ($RVIP_w$) values on the "production" of *w* (BP_d). Coefficients of elasticity α_1, α_2, β_1, β_2 of the production functions in diphtheria and in control were estimated using the method of least squares by Linein statistical software (Excel).

In order to estimate and compare the regimes of control over probability distribution of indices basing on the concept of relative entropy [1,4,8] and control ratio *R* [1,8], analysis of entropy for probability distributions was performed for each index in diphtheria and in the control. Control ratio *R*: $0 \le R \le 1$, it determines the regimen of control over the index and indicates how the system implements the control over probability variability of this index. It is considered that in case of $0 \le R \le 0.1$ control is stochastic, if $0.1 \le R \le 0.3$, then control is quasidetermined, if $0.3 \le R \le 1$, then control is determined [8].

RESULTS

Results of descriptive statistical analysis for diphtheritic and control animals are shown in Table 1. Analysis of changes in *w* (BP_d) and *y* ($RVIP_w$) values suggests that arithmetic means of these values coincided with the control values irrespective of diphtheritic intoxication (Table 1). A minor statistically significant decrease in arithmetic means for *z* (BP_s) and *x* ($LVIP_w$) was observed in diphtheria (compared to the control values).

Paired comparison of coefficients of variation for all indices in diphtheria and in control revealed insignificance of difference, which suggests maintenance of regulatory influences in implementation of functional dependence concerning maintenance of system circulatory dynamics in diphtheria. Paired comparison of skewness and kurtosis for *x* ($LVIP_w$), *y* ($RVIP_w$), *w* (BP_d) in diphtheria and in the control attest to their changes under the influence of diphtheria, which allows to consider these changes as adaptational.

Values of overall coefficients of trivariate correlation r_{xyz} and r_{xyw} for *x* ($LVIP_w$), *y* ($RVIP_w$), *z* (BP_s) and *w* (BP_d) indices were 0.62 and 0.59 ($p<0.05$) in diphtheria and 0.53 and 0.49 ($p<0.01$) in control respectively.

Comparison of tightness of trivariate correlation for the indices in diphtheria and in control using Harrington Verbal Numeric Scale led to an assumption that rabbit cardiovascular system implements its adaptation to heart damage in diphtheria by development of a stronger trivariate correlation of *x* ($LVIP_w$), *y* ($RVIP_w$), *z* (BP_s) and *w* (BP_d) indices, which is fulfilled through the corresponding overall coefficients of trivariate correlation r_{xyz} and r_{xyw}. Thus a stronger trivariate correlation is observed in diphtheria (r_{xyz}=0.62, r_{xyw}=0.59) compared to the control (r_{xyz}=0.53, r_{xyw}=0.49).

TABLE 1. BP_s and BP_d Indices (*M*±*m*)

Index	Diptheria (*n*=17)				Control (*n*=120)			
	BP_s	BP_d	$LVIP_w$	$RVIP_w$	BP_s	BP_d	$LVIP_w$	$RVIP_w$
Arithmetic mean	141.2±9.8	112.6±8.0	89.6±12.3	22.5±2.5	148.7±2.8	114.6±2.5	106.0±5.2	21.4±0.8
Coefficient of variation	0.15	0.15	0.29	0.23	0.11	0.12	0.27	0.2
Skewness	0.62	0.57	0.41	0.02	0.41*	0.02	-0.1	0.8*
Kurtosis	-0.86	-0.55	0.22	-0.03	0.1	-0.3	-0.1	2.63*

Note. *$p<0.05$ compared to 0.

The results of trivariate regression analysis are shown in Table 2.

Values of elasticity coefficients for both LV and RV in diphtheria and in control are positive and vary within 0 and 1. This indicates that IP increase in LV or RV induces the corresponding increase of BP_s. Sufficient inequation $\alpha_1=0.1<<\alpha_2=0.9$ of elasticity coefficients for BPs in the control changed to a more moderate inequation $\alpha_1=0.36<\alpha_2=0.64$ in diphtheria. However, it retained a tendency for a more substantial contribution of RV compared to LV to formation of the *z* (BP_s) value observed in control, in spite of diphtheritic intoxication. The substantial inequation $\beta_1=0.12<<\beta_2=0.88$ of elasticity coefficients for BP_d observed in the control changed to an approximate equation, thus equalizing the contribution of LV and RV to the formation of *w* (BP_d) value in diphtheria.

The equality of the sum of elasticity coefficients to 1 ($\alpha_1+\alpha_2=1$, $\beta_1+\beta_2=1$) is observed in diphtheria and in the control, therefore in spite of diphtheritic intoxication BP_s values are changed to the same proportion as LVIP and RVIP values. This indicates that BP_s production functions retain the constant effect of "production" also in dipththeria, *i.e.* they are Cobb—Douglas functions.

Moreover, on the basis of relative entropy *h* concept and control ratio *R* [1,4] we conducted analysis of entropy of variability of probability distributions for all indices, which allowed to visualize one more regulatory loop of control over probability variability of cardiovascular indices.

Thus, the control ratio *R* for *x* ($LVIP_w$), *y* ($RVIP_w$), *z* (BP_s) and *w* (BP_d) indices in control does not step over the bounds of quasidetermined regime of control over indices (Table 3). This regimen implies some balance between stochastic and determined choice of the control over probabilistic variability of values of these indices. It is the quasidetermined regimen of the control over *x* ($LVIP_w$), *y* ($RVIP_w$), *z* (BP_s) and *w* (BP_d) indices which is used by a live system in control, because it allows adequate maintenance of these values and effective saving of its intrinsic energy [8]. Under the influence of diphtheritic toxin, control ratios for *x* ($LVIP_w$), *y* ($RVIP_w$) indices overrides the quasideterministic bounds and fall into the interval of stochastic regime of control, which attests to an increase in stochasticity of control over these values during realization of integrative interactions and limitation of the use of information by cardiovascular system in order to fulfill control actions. This could explain the fact of decrease of cardiovascular system capacities during its functioning and changes of tightness of pair correlation between LVIP and RVIP indices [7,9].

Moreover, these data suggest that heart failure caused by diphtheria is a consequence of not only direct heart damage, but also of the impairment of information transfer process in the functional system responsible for central hemodynamics and integration interactions.

TABLE 2. Elasticity Coefficients for "Production" of BP_s and BP_d

Coefficient	Diphtheria (*n*=17)	Control (*n*=120)
α_1 for LV	0.36	0.10
α_2 for RV	0.64	0.90
$\alpha_1+\alpha_2$	1	1
β_1 for LV	0.42	0.12
β_2 for RV	0.58	0.88
$\beta_1+\beta_2$	1	1

TABLE 3. Relative Entropy *h* and Control Ratio *R*

	Diphtheria (*n*=17)		Control (*n*=120)	
	h	R	h	R
z (BP_s)	0.9	0.1	0.87	0.13
w (BP_d)	0.88	0.12	0.88	0.12
x ($LVIP_w$)	0.93	0.07	0.82	0.18
y ($RVIP_w$)	0.94	0.06	0.704	0.296

These results suggest that rabbit cardiovascular system implements is adaptation to direct heart damage in diphtheria, including change in tightness of trivariate correlation of $LVIP_w$ and $RVIP_w$ values to BP_s values which can be seen in the corresponding overall coefficients of trivariate correlation r_{xyz} and r_{xyw}.

We also established the fact that the regimen of the control over probability distributions of $LVIP_w$ and $RVIP_w$ indices is changed from quasideteremined to stochastic in diphtheria.

Basing on the empirical production functions of BP_s and BP_d indices we found that the contribution of LVIP and RVIP values into the formation of BP_s and BP_d values is changed in diphtheria compared to the control. However, in spite of diphtheritic intoxication, the production functions of BP_s and BP_d indices show permanent effect of "production", *i.e.* they are Cobb-Douglas functions.

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