PHASE-PLANE PROPERTIES OF PLASMA RENIN ACTIVITY AFTER CAPTOPRIL TREATMENT

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Abstract: The purpose of this study is to analyze renin-angiotensin system after captopril treatment employing the phase-plane method. Dose-dependent mathematical model of the change of plasma renin activity based on a system of nonlinear differential equations is formulated. Analytical expressions for critical points of the modeled process were obtained. The local stability and the type of these points were tested in the function of the administered dose. Data processing and analysis were performed with the Korelia program.

Keywords: plasma renin activity, phase-plane, stability analysis

1. INTRODUCTION

The Renin-Angiotensin System (RAS) is a hormonal system that is involved in regulating blood pressure in the body [1]. When decreasing the kidney juxtaglomerular perfusion, the renin enzyme is released, which in turn cleaves an inactive peptide called angiotensinogen by converting it to angiotensin I [2]. Then, by angiotensin converting enzyme (ACE), angiotensin I is converted to angiotensin II [3]. Angiotensin II is significant bio-active product of the RAS. It acts as an endocrine, autocrine and intracrine hormone.

Plasma renin activity (PRA) is a measure of the activity of renin, determining its production and degradation. The augmentation in renin leads to an increase in angiotensin I and angiotensin II, respectively. The latter suppresses the renin secretion and thus regulates it through negative feedback detailed in [4]. Drugs such as nicardipine and nifedipine stimulate renin release, resulting in an increase in PRA [5]. Due to metabolism, PRA decreases by exponential law. Therefore, a suitable model of PRA change after treatment to these agents is a differential equation of second order [6,7].

Captopril is a widely used antihypertensive drug that inhibits ACE converting angiotensin I to angiotensin II. In this way, it breaks the feedback that affects the secretion of renin. The rate of change of renin is part of the intrinsic growth rate, this

velocity is determined by the marginal quantity of PRA. The same natural law is observed in the angiotensin I degradation process. Therefore, the upward and downward trends in PRA with captopril are approximately symmetric to the extreme value.

The present work aims to analyze the renin-angiotensin system after exposure to various doses of captopril. For this purpose, a dose-dependent mathematical model of the change of PRA based on a system of differential equations reflecting the symmetrical nature of the process is formulated. The model parameters are analyzed by the Phase Plane method.

2. MATHEMATICAL MODEL

2.1. Data acquisition and processing

The experiments were performed on 140 male white Wistar rats. PRA was evaluated radioimmunologicaly (DiaSorin-Biomedica Ltd.) after perorally application of captopril in doses 10, 30, 60, 80 mg/kg body weight (b.w.). Experiment conditions are described in [8]. All of the experiments were conducted according to the Council Directive 2010/63/EU of 22 September 2010 on the protection of animals used for scientific purposes.

Primary data were processed by the statistical program Statistica 12, StatSoft, Inc. and the results are presented as a mean and standard deviation. All other data processing pertaining to the purpose of the present work was performed with the Korelia program [9,10].

2.2. Design of the mathematical model

In order to be possible to model the approximate symmetry of the graph, two simultaneous processes are modeled.

- The first process ***$y_1(t,d)$*** describes the growth of PRA:

$$\frac{dy_1(t,d)}{dt} = r_1(d).\left[1-\frac{y_1(t,d)}{K_1(d)}\right].y_1(t,d) + C_2(d).y_2(t,d) \qquad (1)$$

where:

$r_1(d)$	Rate constant of the process;
$K_1(d)$	Saturation level, depending on dose **d**;
$C_2(d)$	Effective destroying rate - reflects the degree of impact of the second process on the first.

As mentioned above, due to the disruption of the feedback regulating renin secretion, the conversion of angiotensin II is determined by the initial dose of captopril. The decreasing process ***$y_2(t,d)$*** is described with logistic model:

$$\frac{dy_2(t,d)}{dt} = r_2(d).\left[1-\frac{y_2(t,d)}{d}\right].y_2(t,d) \qquad (2)$$

where:

$r_2(d)$	Rate constant of the process;
d	Saturation level, the equivalent on dose **d.**

2.3. Model identification

The parameters in these equations define the identification vector:

$$Q = Q\left(r_1(d), K_1(d), C_2(d), r_2(d)\right) \tag{3}$$

The model is identified using Korelia-Ident program. The identification algorithm is formulated as an optimization task. Model fitting to the experimental data is done applying cyclic coordinate descent method [11]. The calculated values of the identified parameters are presented in Table 1.

Table 1. Identified parameters of the processes

parameters	*Dose [mg/kg] b.w.*			
	10 ◆	*30* ▲	*60* ✳	*80* ●
$r_1(d)$	*0.0029*	*0.0022*	*0.0016*	*0.0014*
$K_1(d)$	*0.193*	*0.144*	*0.114*	*0.112*
$C_2(d)$	*-0.6996*	*-0.4174*	*-0.2229*	*-0.1640*
$r_2(d)$	*-1.60*	*-2.23*	*-2.78*	*-3.03*
Coeff determ. R^2	*0.863*	*0.902*	*0.962*	*0.929*

The graphs of the PRA models for the four doses are shown in Figure 1.

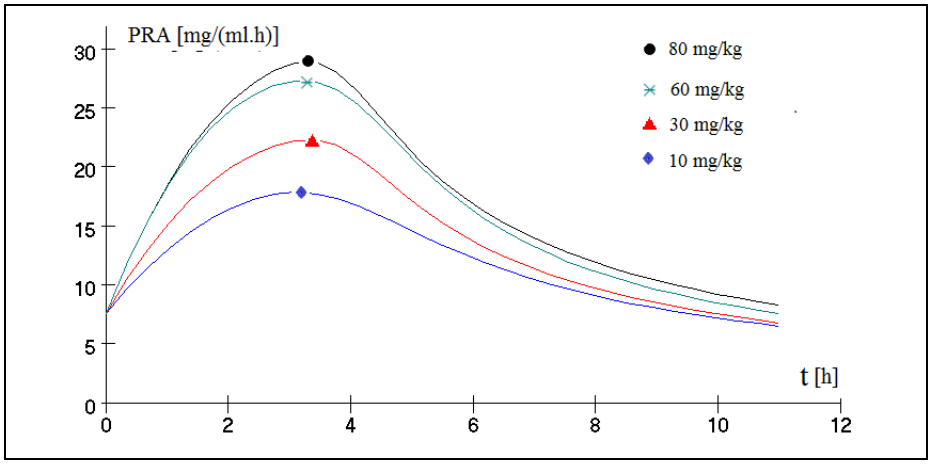


Fig. 1. Graphs of PRA for various doses

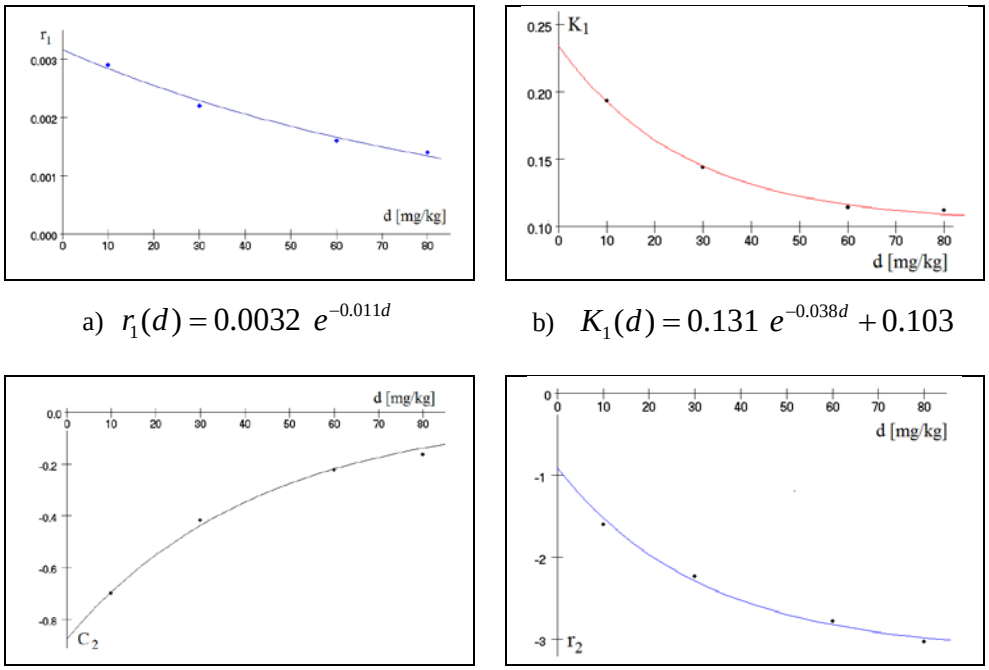
In order to create a dose-dependent PRA model, it is necessary to identify the parameters (3) in function of the dose ***R***. Their graphs are in Figure 2. As seen the

parameters are nonlinear monotone functions. An appropriate function for identifying all four parameters is an exponential equation of the type:

$$f(d) = (C_0 - C_\infty).e^{-r.d} + C_\infty \quad (4)$$

where:
- d – applied dose
- $C_0 = f(0)$ - initial value
- $C_\infty = f(\infty)$ - infinite asymptote
- r – rate constant of the process

The equations of the identified parameters are in Figure 2



a) $r_1(d) = 0.0032\ e^{-0.011d}$

b) $K_1(d) = 0.131\ e^{-0.038d} + 0.103$

c) $C_2(d) = -0.866\ e^{-0.022d}$

d) $r_2(d) = 2.248\ e^{-0.032d} - 3.16$

Fig. 2. Graphs and equations of dose-dependent parameters

Finally, the dose dependent PRA model is described by the system of equations:

$$\begin{cases} r_1(d) = 0.0032\ e^{-0.011d} \\ K_1(d) = 0.131\ e^{-0.038d} + 0.103 \\ C_2(d) = -0.866\ e^{-0.022d} \end{cases} \quad (5)$$

$$\begin{cases} r_2(d) = 2.248\ e^{-0.032d} - 3.16 \\ \dfrac{dy_1(t,d)}{dt} = r_1(d).\left[1 - \dfrac{y_1(t,d)}{K_1(d)}\right].y_1(t,d) + C_2(d).y_2(t,d) \\ \dfrac{dy_2(t,d)}{dt} = r_2(d).\left[1 - \dfrac{y_2(t,d)}{d}\right].y_2(t,d) \end{cases}$$

3. PHASE-PLANE BEHAVIOR

3.1. Autonomous equations in the phase plane and nullclines of the process

The phase plane is defined with the introduction of two new variables $f_1(y_1,y_2)$ and $f_2(y_1,y_2)$ which are independent of t:

$$\begin{cases} f_1(y_1,y_2) = r_1(d).\left[1 - \dfrac{y_1(d)}{K_1(d)}\right].y_1(d) + C_2(d).y_2(d) \\ f_2(y_1,y_2) = r_2(d).\left[1 - \dfrac{y_2(d)}{d}\right].y_2(d) \end{cases} \quad (6)$$

These two functions define the nullclines of the process in the phase plane. Solving the system (6) toward $y_2(d)$, the analytical expressions of nullclines are obtained:

$$y_2(d) = \frac{r_1(d)}{C_2(d)}.\left[1 - \frac{y_1(d)}{K_1(d)}\right].y_1(d) \quad (7a)$$

$$y_2(d) = 0 \quad (7b)$$

$$y_2(d) = d \quad (7c)$$

The graphs of (7a) for the four doses are shown in Figure 3.

3.2. Equilibrium points

The necessary condition of the extreme value is that the derivative of the function becomes zero:

$$\begin{cases} f_1(y_1,y_2) = 0 \\ f_2(y_1,y_2) = 0 \end{cases}$$

From this system, equilibrium points are calculated, in which it is possible to show potential stability or instability of the system. Nullcline (7c) does not intersect

the other two and (7b) coincides with abscissa. After solving the system (7a, b) the following dose-dependent equilibrium points are obtained:

$$\left| \begin{array}{l} y_1 = 0 \\ y_2 = 0 \end{array} \right| \qquad \left| \begin{array}{l} y_1 = K_1(d) \\ y_2 = 0 \end{array} \right| \tag{8}$$

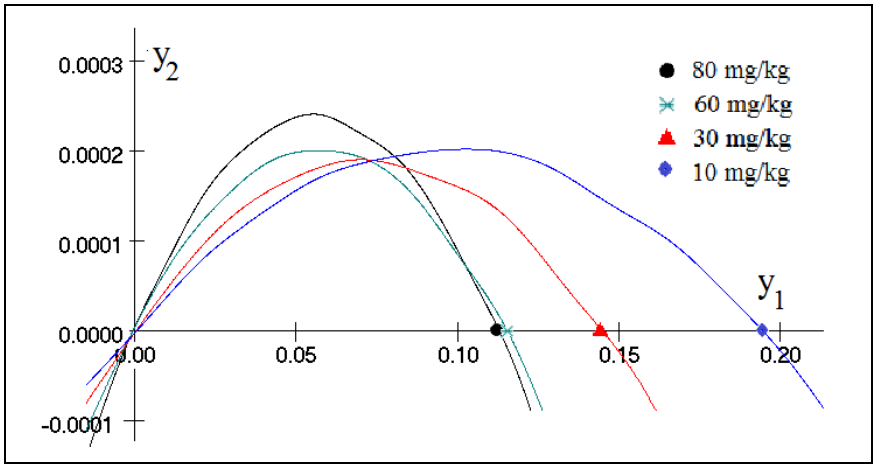


Fig. 3. Nullclines and equilibrium points

3.3. Eigenvalues of the Jacobian

Since the system is non-linear, it is linearized in the vicinity of the critical points to apply the linearized stability criterion. The Jacobian system is:

$$J(d) = \left| \begin{array}{cc} \dfrac{r_1(d).\left(K_1(d) - 2.y_1(d)\right)}{K_1(d)} & -C_2(d) \\ 0 & \dfrac{r_2(d).\left(d - 2.y_2(d)\right)}{d} \end{array} \right| \tag{9}$$

The stability in equilibrium points is determined by looking at the eigenvalues of the characteristic equation:

$$\det\left(J - \lambda.I\right) = \left| \begin{array}{cc} \dfrac{r_1.\left(K_1 - 2.y_1\right)}{K_1} - \lambda & -C_2 \\ 0 & \dfrac{r_2.\left(d - 2.y_2\right)}{d} - \lambda \end{array} \right| = 0 \tag{10}$$

The solutions for eigenvalues of the Jacobian in analytical form are:

$$\left\| \begin{matrix} \lambda_1(y_1, y_2) \\ \lambda_2(y_1, y_2) \end{matrix} \right\| = \left\| \begin{matrix} \frac{r_1(d).\left[K_1(d) - 2.y_1(d)\right]}{K_1(d)} \\ \frac{r_2(d).\left[d - 2.y_2(d)\right]}{d} \end{matrix} \right\| \tag{11}$$

The simultaneous examination of the eigenvalues obtained for each of the peculiar points gives the type of its stability.

4. DISCUSSIONS

4.1. Nullclines of the process

For each administered dose, two nullclines are obtained which have intersections. One coincides with the abscissa axis and the other is the parabola. A specific point of the parabola is its peak ***P(y₁,y₂)***, since it determines the inflection point of the first process. Its coordinates are:

$$P(y_1, y_2) = \left(\frac{K_1}{2}, \frac{K_1.r_1}{4.C_2} \right) \tag{12}$$

It is seen that the saturation level K_1 and destroying rate C_2 are relevant to this point. When $y_1 < K_1/2$, PRA increases with positive acceleration. When passing this point, i.e. half of the saturation level is exceeded; the acceleration is negative, resulting in a decrease in the rate of PRA growth.

4.2. Equilibrium points

The equilibrium state is stable if the real parts of the eigenvalues satisfy the following condition:

$$\left(\mathrm{Re}(\lambda_1) < 0\right) \; AND \; \left(\mathrm{Re}(\lambda_2) < 0\right) \tag{13}$$

As is clear from the solution (11), the eigenvalues are dependent on the dose of the administered drug. After substitution with the coordinates of equilibrium points, the specific eigenvalues defining the type of stability are obtained.

The first critical point ***(0,0)*** defines the following eigenvalues of the Jacobian:

$$\left\| \begin{matrix} \lambda_1 \\ \lambda_2 \end{matrix} \right\| = \left\| \begin{matrix} r_1(d) \\ r_2(d) \end{matrix} \right\| \tag{14}$$

By examining the behavior of these solutions as a function of the increasing dose, is obtained:

$$\lim_{d\to\infty}\lambda_1 = \lim_{d\to\infty}\left(r_1(d)\right) = \lim_{d\to\infty}\left(0.0032e^{-0.011d}\right) = {}^{+}0 > 0 \quad (15)$$

$$\lim_{d\to\infty}\lambda_2 = \lim_{d\to\infty}\left(r_2(d)\right) = \lim_{d\to\infty}\left(2.248e^{-0.032d} - 3.16\right) = -3.16 < 0 \quad (16)$$

Eigenvalues with different signs are an indication of a saddle point. This means that each dose $d > 0$ will cause an increase in PRA.

The second critical point is with coordinates $(K_1(d),0)$. Only the first coordinate is dose-dependent, and after algebraic transformations, negative values for λ_1 are obtained for the entire dose range:

$$\lim_{d\to\infty}\lambda_1 = \lim_{\substack{d\to\infty \\ y1=K1}}\frac{r_1(d).\left[K_1(d) - 2.y_1(d)\right]}{K_1(d)} = \lim_{d\to\infty}\left(-r_1(d)\right) = {}^{-}0 < 0 \quad (17)$$

Both of eigenvalues are negative numbers, which defines the second critical point as a stable node. This ensures that of slight perturbations the process remains in the vicinity of this point. In Table 2 are the analytical values of eigenvalues and the type of singularity.

Table 2. Type of equilibrium points

Equilibrium points	Eigenvalues	Type of singularity
$(y_1,y_2) = (0,0)$	$\left\|\begin{matrix}\lambda_1 \\ \lambda_2\end{matrix}\right\| = \left\|\begin{matrix}r_1(d) > 0 \\ r_2(d) < 0\end{matrix}\right\|$	Saddle point
$(y_1,y_2) = (K_1(d),0)$	$\left\|\begin{matrix}\lambda_1 \\ \lambda_2\end{matrix}\right\| = \left\|\begin{matrix}-r_1(d) < 0 \\ r_2(d) < 0\end{matrix}\right\|$	Stable node

It can be seen that the values of eigenvalues depend only on the rate constant r_1 of the process $y_1(d)$.

5. CONCLUSION

In this study the stability analysis of renin-angiotensin system after captopril treatment was investigated employing the method of phase portrait analysis.

A dose-dependent model of PRA change has been formulated. The fact that captopril breaks down the feedback regulating renin secretion, has been taken into account. This implies a model represented by two processes, each of which is a nonlinear first-order equation.

An identification vector of four-parameter has been formulated. An identification of the system of equations for the four doses of the agent was done and a dose-dependent model of PRA was obtained.

Applying the phase plane method nullclines of the models are built. Their intersections set the critical points in which the process stability is examined. Analytical expressions for the two equilibrium points were obtained in function of the administered dose.

The first critical point is the origin of the phase plane. The second point has an abscissa equal to the saturation level for the respective dose.

The local stability and type of the two critical points in function of the administered dose were investigated. For this purpose, a linearized system Jacobian was obtained and its eigenvalues were calculated. It is shown that they depend only on the rate constant of the first process.

The eigenvalues determine the first point as a saddle point type. This is the unstable process point. Applying any dose of the preparation results in disturbing the balance of the PRA.

The second critical point is a stable node - in small disturbances, the process remains in the vicinity of that point.

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