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Identification of Regulatory Mechanism of Orthostatic Response

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Abstract*—*En bloc assumes modeling all phases of the orthostatic test with the only one mathematical model, which allows the complex parametric view of orthostatic response. The work presents the implementation of a mathematical model for processing of the measurements of systolic, diastolic blood pressure and heart rate performed on volunteers during orthostatic test. The original assumption of model hypothesis that every postural change means only one Stressor, did not complying with the measurements of physiological circulation factor-time profiles. Results of the identification support the hypothesis that second postural change of orthostatic test causes induced Stressors, with the observation of a physiological regulation mechanism. Maximal demonstrations are on the heart rate and diastolic blood pressure-time profile, minimal are for the measurements of the systolic blood pressure. Presented study gives a new view on orthostatic test with impact on clinical practice.

Keywords*—*En bloc modeling, physiological circulatory factor, postural change, stressor.

I. Introduction

IMPLEMENTATION of appropriate mathematical models to identification, of commonly performed screening tests, plays the urgent role in clinical practice in the twenty-first century. Measurements of a physiological circulatory factor (PCF)-time profile, such as the systolic blood pressure (SP), diastolic blood pressure (DP) and heart rate (HR)-time profiles, are important, but present only the indicative value in general practitioner's office in the evaluation of response to the postural change during a orthostatic test [1]-[4].

Orthostatic test generally consists of the three phases. *Adaptation* is the first phase and presents the initial stabilization to reaches a basal steady state. *Activation* is the second phase and includes one or more postural changes. *Recovery* is the last phase of the orthostatic test with last postural change and condition for reach the basal steady state, Fig. 1.

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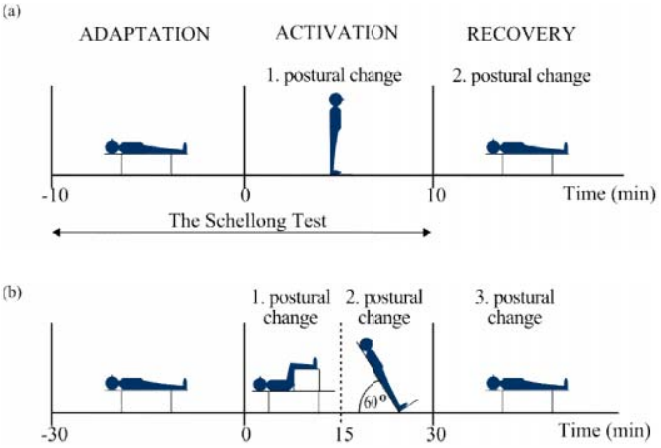

Fig. 1 The general scheme of orthostatic tests (a) Schellong test (b) Tilt-table test

Schellong test [5] in Fig. 1 (a), as the first known orthostatic test, has been designed to derive so-called normal behavior from a hypotonic or hypodynamic character as disturbance in circulatory regulation [6]. Fig. 2 [5], [6] shows determination of the differences in SP, DP and HR during the *adaptation* and the *activation* of the Schellong test.

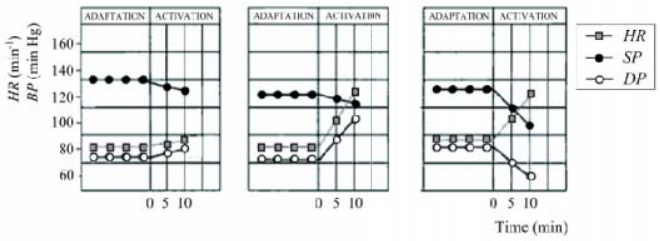

Fig. 2 Schellong's original criteria for determining circulatory behavior in healthy person (left), patient with hypotonic dysregulation (middle), and (right) with hypodynamic dysregulation. t = time; BP = blood pressure; HR = heart rate; SP = systolic blood pressure; DP = diastolic blood pressure; (Figure adapted from the original [5], [6]).

Currently known as the Tilt-table testing [1], [3], [4], Fig. 1 (b) is based on the same principle for assessing the response to change in posture. There are many protocols of the Tilt-table test differing from each other, e.g. assembling design, duration or possibly of the pharmacological provocation [1].

The purpose of this study was to create a model of the orthostatic response *en bloc* and quantification of relationships between a *stressor*, as a stimulus and a *stress*, like a possible consequence of ill-health [7]-[9]. *En bloc* assumes modeling

all phases of the orthostatic test with the only one mathematical model, which allows the complex parametric view of orthostatic response. It is supposed that each postural change independently represents only one *stressor*, whose unknown intensity of affecting the measurable PCF.

II. Subjects and Methods

A. Protocol of the Study

The research purpose of the orthostatic response study was realized by the Laboratory of Human Endocrinology in the Institute of Experimental Endocrinology of the Slovak Academy of Sciences (SAS) in Bratislava, Slovakia [9]-[12]. Six young male subjects with confirmed diagnosis of hypertension (HT) (age: 22.3±3.9 years; body mass index (BMI): 24.7±3.5kg·m^{-2}), and nine young healthy male subjects with similar BMI (age: 23.7±4.4 years; BMI: 22.2±2.1kg·m^{-2}) and normal blood pressure served as controls (K), were studied.

Fig. 1 (b) shows the design of the Tilt-table testing protocol, revised by the Laboratory of Human Endocrinology, SAS. Time duration of each phase is 30min without pharmacological provocation. Test composed of two postural changes in the second *activation* phase. The investigation started between 07:30 and 08:00h after an overnight fast. The *adaptation* phase presents the subject in the supine position for 30min. The *activation* phase in t = 0min, Fig. 1 (b), as hypothetic Stressor 1, means the subject placed in the supine position with the legs placed on a pad and the knees in 90° flexion [10]. After 15min follows the tilting of the subject bed to 60° like hypothetic Stressor 2 and second postural change in the *activation* phase. At the time of 30min, in the third *recovery* phase, the subject is in the supine. The last postural change assumed the hypothetic Stressor 3. The measurements of SP, DP and HR values were performed by an automated monitor Critikon DINAMAP ® COMPACT Model T (Criticon, Inc.; Tampa; FL, USA). The scheme of the PCF measurement running within the times t = 0; 15; 16; 17; 20; 25; 30; 45min.

The study was approved by the Ethics Committee of the Institute of Experimental Endocrinology, SAS, Bratislava, Slovakia and the informed written consent was obtained from all subjects [12].

B. En Bloc Modeling

The system approach, as the basic principle processing of the measurements on the dynamic systems, gives the assumption to successful processing of the individual protocols of the orthostatic test. The classifications of the systems, as the first step of the system approach to processing *en bloc* of the orthostatic response, expected to define the input $I(t)$ and the output $V(t)$ functions on the observed system, where t presents the time. The systems, defined by input-output functions, will be further considered as continual, linear dynamic systems [13].

We assume the input function, as the intensity $I(t)$ of stressor/stressors respectively, induced by the change of posture; the output function $V(t)$, as measured by changes of PCF, such as SP, DP and HR-time profiles, individually. The increase ΔV of the measured PCF in the time t, as the result of stress load during the postural change, can be described (1)

$$\Delta V(t) = V(t) - V_0 \tag{1}$$

V_0 is the basal PCF value in the time t = 0 min, affected by the appertaining tested protocol. Fig. 3 represents the input-output definition of observed system S [14].

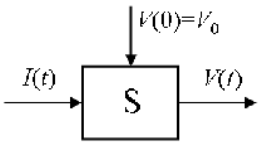

Fig. 3 The input-output definition of system S. t = time, $I(t)$ = input function of system S, $V(t)$ = output function of system S, V_0 = basal value of measured PCF in the time of t = 0min

By the input function $I(t)$ describing the *stressors* intensities-time profile, the input-output definition of observed system S can be written (2)

$$H(s) = \frac{\Delta V(s)}{I(s)} \tag{2}$$

as the ratio of Laplace expression of output $\Delta V(s)$ and input $I(s)$ system functions, where $H(s)$ is the transfer function of the system and s is Laplace operator.

The simplest mathematical model of the linear dynamic system presents the model in the form of transfer function of the model $H_M(s)$ (3)

$$H_M(s) = \frac{G}{1+Ts} \tag{3}$$

where G is the gain of the system identified the static properties of system in steady state, T is the time constant identified the dynamic properties of system [13].

In the case of assumption of input function $I(t)$ is valid the form (4)

$$I(t) = \begin{cases} 0; \text{ for } t \le 0 \\ I_1; \text{ for } t \in (0, t_s] \\ I_2 = 0; \text{ for } t > t_s \end{cases} \tag{4}$$

I_1 is the intensity of Stressor 1 in the *activation* phase and I_2 is the intensity in the *recovery* phase, Fig. 4 (a).

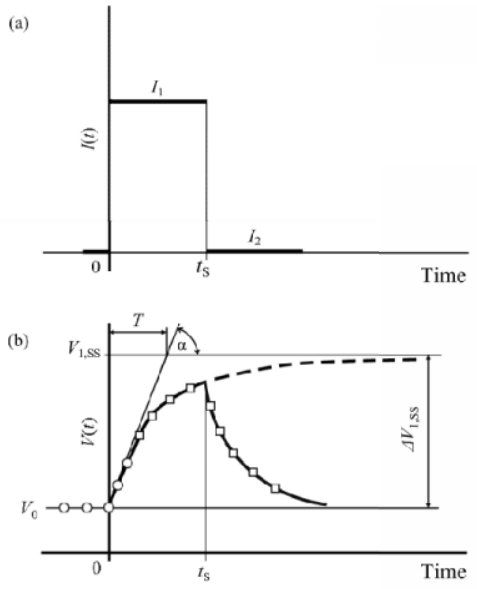

Fig. 4 The system approach to orthostatic test (a) the input function $I(t)$ and (b) the output function $V(t)$. V_0 = the basal value of measured PCF, $V_{1,SS}$ = the value of PCF in hypothetic steady state, $\Delta V_{1,SS}$ = increase of PCF value in hypothetic steady state, α = angle of the tangent in the time $t = 0$ min in the point $[0, V_0]$, T = time constant, circles = measured values according to Schellong, squares = measured values according to extended sampling scheme, full line = model solving in the form of differential equation (6) for the input function (4)

As the intensity I_1 of Stressor 1 is not known, therefore it was not possible to estimate the gain G of the system only from measured data values. From this reason the parameter G has to be consider as $G = 1$ and the transfer function of the model in the form (5)

$$H_M(s) = \frac{1}{1+Ts} \tag{5}$$

Then the intensity value I_1 of Stressor 1 can be interpreted as the increase $\Delta V_{1,SS}$ of steady state of measured value PCF, such as SP, DP and HR, individually.

There is valid the increase $\Delta V_{SS} = \Delta V(t)$ in time $t \to \infty$ during the effect of *stressor* with the intensity $I(t)$ to the steady state where $\Delta V(t)$ [14] is the solution of differential equation (6) for the input function $I(t)$ (4).

$$\Delta V(t) + T\frac{d\Delta V(t)}{dt} = I(t),\ \Delta V(0) = 0 \tag{6}$$

Fig. 4 (b) describes the predicted reaction of the hypothetic system presented by (4) and (6). From initially three measurements (circles), the scheme of extended sampling contains seven measurements in the *activation* phase of the orthostatic test. Comparing of Fig. 2 and Fig. 4 (b) is seen, that the evaluation of the original Schellong test (Fig. 2) means only measured profile of the initial phase by circles marked in Fig. 4 (b). From the system approach, the evaluation of the Schellong test (Fig. 2) gives the information about the time constant T with the validity that $T = tg\ \alpha$, where α is the angle between increase/decrease of the measured value PCF and the timeline in the initial time of the *activation* phase of the test. The system evaluation *en bloc*, Fig. 4 (b), enables to estimate the static properties of the system by the parameter $\Delta V_{1,SS}$ indicating the system behavior in steady state in the case of long-term influence of Stressor 1, besides the estimation of time constant T indicating the mean time effect of Stressor 1.

For the analytical solution of the model (6) then holds (7)

$$\Delta V(t) = \begin{cases} I_1\left(1 - e^{-\frac{t}{T}}\right);\ \text{pre } t \le t_s; \\ I_1\left(1 - e^{-\frac{t_s}{T}}\right)e^{-\frac{t-t_s}{T}};\ \text{pre } t > t_s \end{cases} \tag{7}$$

The vector of estimated parameters λ of the model (6) of orthostatic test with one postural position in *activation* phase has the form (8)

$$\lambda = (T, I_1, I_2) \tag{8}$$

The model of the orthostatic test of the Laboratory of Human Endocrinology, SAS, Bratislava, with the hypothesis H1 that one postural change means one *stressor*, is shown in Fig. 5.

For the analytical solution of the model (6) is valid (9)

$$\Delta V(t) = \begin{cases} 0;\ \text{for } t \le 0 \\ \sum_{i=0}^{n-1}\left(I_{i+1} - I_i\right)\left(1 - e^{-\frac{t-t_i}{T}}\right)\ \text{for } t_0 = 0; I_0 = 0 \end{cases} \tag{9}$$

where $n = 3$ is the number of *stressors*, I_i are estimated intensities values within the time intervals $[t_i, t_{i+1}]$ by the effect of *stressors* for $i = 0, ..., n-1$.

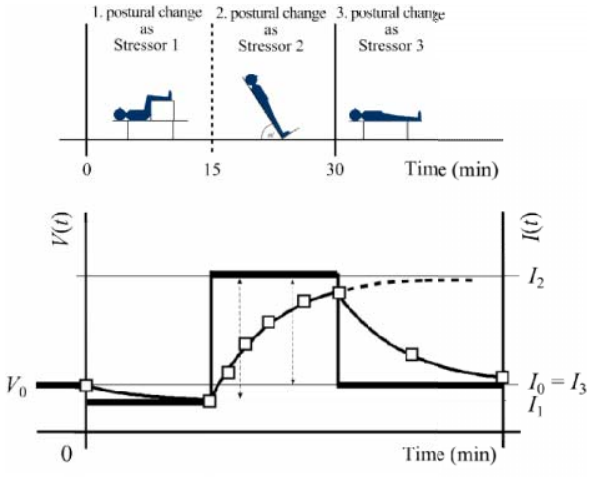

Fig. 5 The model of the orthostatic test with the hypothesis H1; $I(t)$ = time course of the input function $I(t)$, resp. the output function $V(t)$ with the measured values PCF points

The vector of estimated parameters λ of the model of the postural test with presented hypothesis H1 has the form (10)

$$\lambda_{H1} = (T, I_i; i = 1,2,3) \tag{10}$$

where estimated parameter I_i quantifies the intensity of the effect of individual Stressors 1, 2 and 3, respectively. T is the time constant of system.

The assumed hypothesis H1 of the model that one postural change means one *stressor* with estimated intensity I did not complying with the measurements of PCF-time profiles. Consequently was proposed the model of orthostatic test with hypothesis H2 expressed that the second postural change causes induced *stressors*. Fig. 6 (a) describes the input function $I(t)$ process in the case that the second postural change in the *activation* phase of orthostatic test causes Stressors 2, 3 and 4. Fig. 6 (b) shows the model output function $V(t)$ with observed regulation mechanism respected induced Stressors 3 and 4.

In the case of the assumption that the second postural change causes besides Stressor 2 also two induced Stressors 3 and 4, then the number of estimated parameters increases to four, i.e. two estimated intensities I_3, I_4 and two intervals of their effect, their starting times t_2 and t_3, respectively, Fig. 6. The analytical solution of the model (6) for the hypothesis H2 with the number n = 5 of *stressors* analogously as for hypothesis H1 is valid (9).

The vector of estimated parameters λ of the model related to hypothesis H2 has the following form (11)

$$\lambda_{H2} = (T, I_i; i = 1,2,3,4,5; t_j, j = 2,3) \tag{11}$$

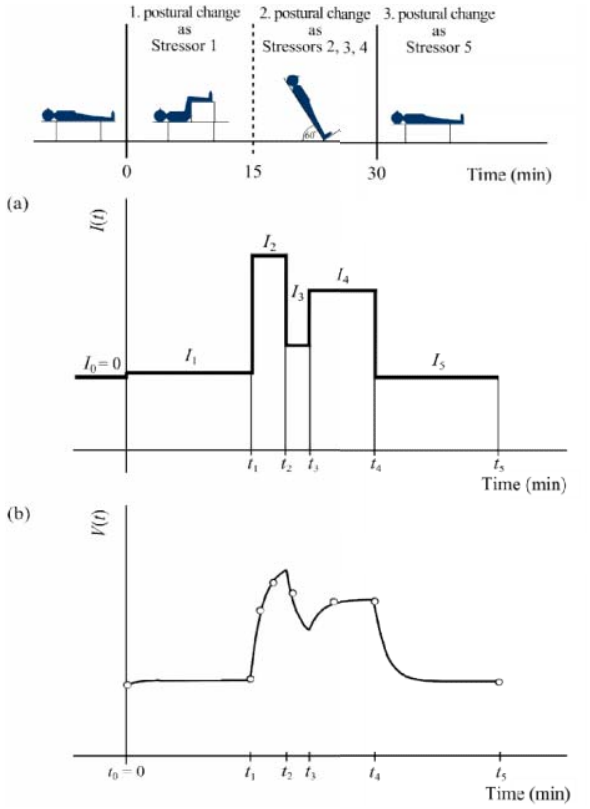

Fig. 6 The model of orthostatic test with hypothesis H2; (a) $I(t)$ = time course of the input function, resp. (b) the output function $V(t)$ with the two induced stressors of subject K2

As seen (9), from the viewpoint of estimated parameters of vectors λ_{H1} a λ_{H2}, it represents the nonlinear model of measurement. The parameters estimation of the vectors λ_{H1} and λ_{H2} were performed by optimization method type Monte Carlo. For the computing simulation and the calculation of the parameters estimation of vectors λ_{H1} and λ_{H2} model (6) for the hypothesis H1 and H2, was used the software CTDB (Clinical Trials DataBase) [13].

III. Results

Table I includes the results of the identification of regulatory mechanism of orthostatic response for measurements of the heart rate (HR)-time profiles in connection with Fig. 6 related to the subjects of tested control group (K) and group with confirmed diagnosis of hypertension (HT) of orthostatic test. Figs. 7 and 8 represent measured time changes of physiological circulatory factors as systolic blood pressure (SP), diastolic blood pressure (DP) and heart rate (HR). The processing of the orthostatic test measurements of other subjects of both groups looks each other as analogous. Identified regulatory mechanism, quantified as induced *stressors*, was showed to at least on the systolic blood pressure time profiles, Figs. 7 (a) and 8 (a), for both subject groups. Figs. 7 (b) and 8 (b) show identified manifestations of induced *stressors* on the diastolic blood pressure time profiles. The maximal manifestation was observed on the heart rate time profile, Figs. 7 (c) and 8 (c).

TABLE I
THE ESTIMATED PARAMETERS VALUES OF VECTOR Λ_{H2} WITH INDUCED REGULATION MECHANISM FOR MEASUREMENTS OF THE HEART RATE-TIME PROFILE
(a)

Code	T (min)	HR (0) (min^{-1})	$\Delta HR_{1,SS}$ (min^{-1})	t_2 (min)	$\Delta HR_{2,SS}$ (min^{-1})	t_3 (min)	$\Delta HR_{3,SS}$ (min^{-1})	$\Delta HR_{4,SS}$ (min^{-1})	$\Delta HR_{5,SS}$ (min^{-1})
2	1.19	52	2.52	16.85	54.78	24.33	-42.56	29.32	-41.63
4	2.64	69	-6.69	17	54.43	24.12	-28.57	19.97	-44.31
6	2.21	65	-2.97	16.51	64.85	19.29	-76.58	26.61	-20.15
9	1.39	62	-0.89	16.26	78.11	25	-50.44	7.51	-36.26
10	1.25	43	0	16.58	40.36	25.01	-16.38	6.07	-27.96
19	2.31	66	1.28	16.23	11.27	18.16	-16.69	16.03	-10.92
20	1.83	66	-3.87	19.17	29.94	22.24	-24.52	9.46	-19.51
24	1.02	48	2.03	19.82	54.53	21.74	-36.65	26.45	-43.1
30	2.69	55	-3.95	16.05	105.38	24.3	-74.14	10.69	-46.07
Mean	1.84	58.44	-1.39	17.16	54.85	22.69	-40.73	16.90	-32.21
SD	0.61	8.71	2.97	1.29	25.66	2.39	21.34	8.49	12.20

(b)

Code	T (min)	HR (0) (min^{-1})	$\Delta HR_{1,SS}$ (min^{-1})	t_2 (min)	$\Delta HR_{2,SS}$ (min^{-1})	t_3 (min)	$\Delta HR_{3,SS}$ (min^{-1})	$\Delta HR_{4,SS}$ (min^{-1})	$\Delta HR_{5,SS}$ (min^{-1})
1	1.58	65.00	-0.86	17.24	58.33	22.61	-49.42	17.98	-28.04
12	1.93	64.00	-0.18	19.44	20.28	24.90	-17.94	4.79	-17.68
16	1.41	64.00	-0.88	15.89	-9.27	24.85	25.78	-15.23	-9.33
17	1.50	57.00	-7.03	18.30	24.63	25.13	0.00	0.00	-24.59
27	1.35	59.00	-2.53	16.70	37.56	18.56	-27.54	14.01	-23.46
35	1.35	62.00	0.00	22.99	24.88	25.60	-14.18	14.78	-25.42
Mean	1.52	61.83	-1.91	18.43	26.07	23.61	-13.88	6.06	-21.42
SD	0.20	2.91	2.43	2.33	20.24	2.45	23.21	11.35	6.25

K = health subjects, (b) HT = subjects with untreated hypertension,

T = time constant, HR = heart rate, HR (0) = measured the basal heart rate values in $t = 0$, I_i = estimated parameters interpreted as $\Delta HR_{i,SS}$ values for $i = 1,.., 5$, of the individual *stressors*, including induced *stressors*, during the measurements of HR profile in steady state of the orthostatic test; t_2 and t_3 = estimated parameters as starting times of induced Stressor 3 and Stressor 4, Mean = mean value, SD = standard deviation.

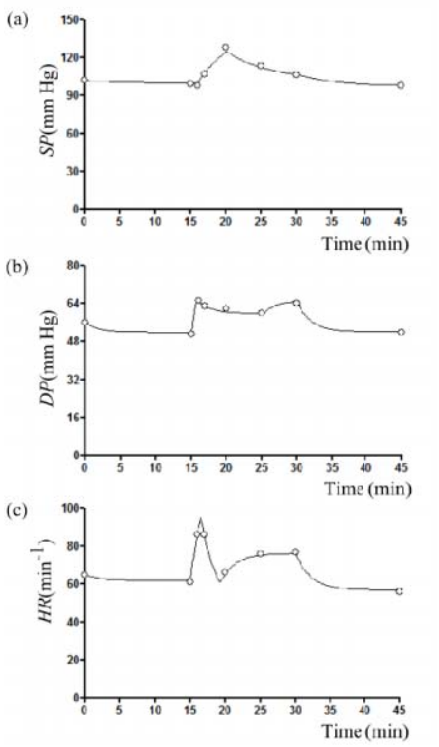

Fig. 7 The modeling results of subject K6 from the control group. Points = measured time changes PCF: (a) systolic blood pressure SP, (b) diastolic blood pressure DP, (c) heart rate HR, by the effect of postural changes 1, 2 and 3, curve = model of hypothesis H2

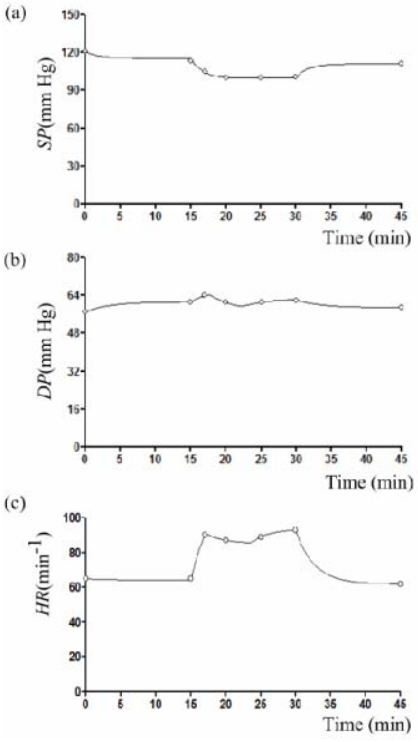

Fig. 8 The modeling results of subject HT1 from the hypertonic group. Points = measured time changes PCF: (a) systolic blood pressure SP, (b) diastolic blood pressure DP, (c) heart rate HR, by the effect of postural changes 1, 2 and 3, curve = model of hypothesis H2

IV. Discussion

The main aim of this study is the identification of regulatory mechanism of the orthostatic response, which minimizes the achievement of extreme high values of the diastolic blood pressure and the heart rate in the orthostatic test.

Developing of mathematical models of observed system and distinguishing of dynamic and static properties of linear dynamic models on tested system can present the important contribution for the better specification of diagnosis associated with orthostatic dysregulation [15]-[18].

Acknowledgment

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