A Prediction Model of Blood Pressure Using Endocrine System and Autonomic Nervous System

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ABSTRACT - Hypertension is a medical problem with no permanent cure. Extended hypertension can cause various cardio vascular diseases, cerebral vascular diseases, and circulatory system trouble. Medical treatment at present does not consider circadian variation of blood pressure in patients ; therefore, the problem of over-reduction of blood pressure through drugs sometimes occurs. This paper presents a prediction model of circadian variation of mean blood pressure employing the endocrine grand and the autonomic nervous system.

1. INTRODUCTION

The autonomic nervous system and the endocrine glands in mammals have circadian variation [1] during periods of sleep and non-sleep. These circadian variations are formed on suprachiasmatic nuclei in the hypothalamus [2]. Blood pressure is regulated by the endocrine glands and the autonomic nervous system. Blood pressure varies as regulated by breathing (short-term) and circadian variation (long-term).

Hypertension for extended periods can cause various cardio vascular diseases, cerebral vascular diseases and circulatory system trouble. Drugs composed of a β-blocker are used as the common medical treatment in hypertension.

It is reported that myocardial infarction and cerebral hemorrhage occur due to rising blood pressure before awakening in the early morning [1], and that cerebral infarction occurs at rest at night [3]. Since medical treatment at present does not consider circadian variation of blood pressure in patients, there is a problem of over-reduction of blood pressure by employing drugs [1]. It would be useful for preventing harm to internal organs, if the variation of blood pressure could be predicted after drug administration. Then, a proper plan of treatment, including drugs, can be provided.

This papor presents a prediction model of circadian variation of mean blood pressure employing the endocrine glands and the autonomic nervous system. Heart rate and mean blood pressure in 17 normal subjects and 17 essential hypertensive subjects are simulated by employing a model. The absolute errors between simulation results and measured values are calculated to evaluate the model.

2. REGULATION OF MEAN BLOOD PRESSURE BY THE ENDOCRINE GLANDS AND AUTONOMIC NERVOUS SYSTEM

<2-1> Regulation of Mean Blood Pressure by Medulliadrenal Hormones

Table 1 shows body chemicals which affect the regulation of mean blood pressure. There are two endocrine glands in the adrenal gland. The inside of an adrenal gland is called adrenal medulla, and its outside is called the adrenal cortex. Blood of the adrenal gland flows into the adrenal medulla through the adrenal cortex. The adrenal medulla is stimulated by exciting the sympathetic nervous system and angiotensin , after which medulliadrenal hormones are secreted into blood.

Medulliadrenal hormones are composed mainly of adrenaline and noradrenaline. Adrenaline stimulates the cardio accelerator center, increases heart rate and dilates peripheral blood vessels. Noradrenaline stimulates the cardio accelerator center and contracts peripheral blood vessels. Noradrenaline is changed into adrenaline by glucocorticoid, which is secreted from the adrenal cortex.

<2-2> Regulation of Mean Blood Pressure by Adrenocortical Hormones

The adrenal cortex is stimulated by adrenocorticotrophic hormones and angiotensin , after which adrenocortical hormones are secreted into the blood. Adrenocortical hormones are composed of glucocorticoids and mineralocorticoids. Glucocorticoid is secreted in the adrenal cortex, then it is transmitted to the adrenal medulla. Glucocorticoid changes noradrenaline to adrenaline, which is one of the components that regulates mean blood pressure.

Aldosteron, which is a mineralocorticoid, also regulates mean blood pressure. Aldosteron has an influence on the uriniferous tubule in kidney in that it promotes the reabsorption of natrium ion and water. As a result, venous return, cardiac output per minute, and mean blood pressure are increased, respectively.

<2-3> Regulation of Mean Blood Pressure by Anglotensin II

AnglotensinII may bring on a four-fold increase of vasoconstriction [4] compared to

noradrenaline. Angiotensin II stimulates the adrenal cortex and adrenal medulla, then promotes the secretion of adrenocortical hormones and medulliadrenal hormones.

<2-4> Regulation of Mean Blood Pressure by the Autonomic Nervous System

Heart rate and stroke volume are regulated by the cardio accelerator center and cardio inhibitory center. Cardiac output per minute is regulated by controlling heart rate and stroke volume.

Peripheral resistance is controlled by the vasomotor center, which is regulated by stimulation of the vasochemo receptor and baro receptor. Thus, cardiac output per minute and peripheral resistance are regulated, thus mean blood pressure is also regulated.

3. MODEL OF MEAN BLOOD PRESSURE

<3-1> Submodel of Endocrine System

Changes of the adrenocorticotrophic hormone have circadian variations [5],[6], which tend to bring on the maximum value in the morning and minimum value in the evening. Angiotensin has a circadian variation [7] which has a high value during daytime activity and a low value during nighttime rest. The submodel is based on circadian variations of adrenocorticotrophic hormone and angiotensin .

A submodel of the endocrine system is shown in Fig. 1. Input signals of the submodel are circadian variations of adrenocorticotrophic hormone and angiotensin hormone on circadian variation ACTH(t) is expressed as the equation (1)

$$ACTH(t)=A_a\{\sin(2\pi t/T_a+\phi_a)+1\} \quad (1)$$

A_a is the amplitude of circadian variation, T_a is the period of circadian variation, ϕ_a is the phase difference between 0 a.m. and any given time, and t is any given time.

The activity level of human is expressed as the pressure rate product (PRP), which is the product of heart rate and mean blood pressure. Therefore, circadian variation of angiotensin is expressed as equation (2) by using heart rate $HR_e(t)$ and mean blood pressure $MBP_e(t)$, all of which are obtained by measurements.

$$A(t) = HR_e(t)*MBP_e(t)/100 \quad (2)$$

Aldosteron accelerates cardiac output per minute. Glucocorticoid increases adrenaline and decreases noradrenaline. Adrenaline mainly stimulates the cardio accelerator center, and noradrenaline mainly increases peripheral resistance. Adrenaline is an input value for the cardio accelerator center, and noradrenaline is an input value for peripheral resistance. Angiotensin increases peripheral resistance. Therefore, noradrenaline and angiotensin are synthesized as input values of peripheral resistance in this submodel.

<3-2>Submodel of the Autonomic Nervous System

A submodel of the autonomic nervous system is shown in Fig. 2. Input values of the submodel are changed values of the cardio

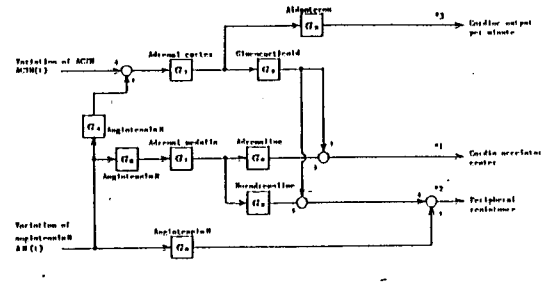

Fig.1 Submodel of endocrine system.

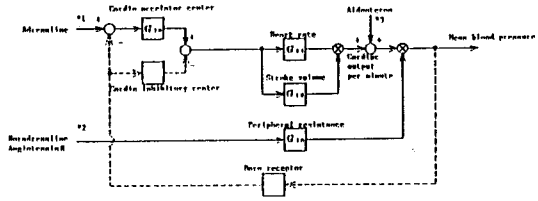

Fig.2 Submodel of autonomic nervous system.

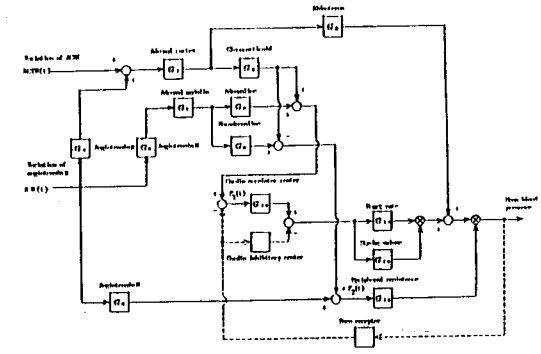

Fig.3 Model of mean blood pressure.

accelerator center (*1 in Fig. 2), peripheral resistance, *2 in Fig. 2 and *3 in Fig. 2, respectively.

Stimulation of the cardio accelerator center is obtained from the change of input values. The stimulation changes heart rate and stroke volume. Cardiac output per minute is obtained by multiplying heart rate by stroke volume. Multiplying peripheral resistance values by the sum of cardiac output per minute and the increased value of cardiac output per minute stimulated by aldosteron obtains mean blood pressure.

Body Chemicals	Effects
Adrenaline	1. Increases heart rate. 2. Dilates peripheral vessels.
Noradrenaline	1. Contracts peripheral vessels. 2. Decreases heart rate by baro refrex action.
Glucocorticoid	Changes noradrenaline to adrenaline.
Aldosteron	Promotes the reabsorption of natrium ion and water, and increases venous return, cardiac output per minute, and mean blood pressure.
Angiotensin II	1. Contracts peripheral vessels. 2. Stimulates the adrenal cortex and adrenal medulla, and promotes the secretion of adrenocortical hormones and medulliadrenal hormones.

Table 1 Effect of adrenaline, noradrenaline, glucocorticoid, aldosteron, and angiotensin 2.

In the submodel, it is assumed that the affect from the baro receptor to the change in circadian variation of the mean blood pressure is small. The baro receptor is neglected in the submodel. Since a signal transmission from the center to the cardio inhibitory center is only a synapse transmission, the endocrine system does not affect the cardio inhibitory center. The cardio inhibitory center is neglected in the submodel. It is assumed that the carbon dioxide density in blood keep a constant value. The vasochemo receptor is neglected in the submodel.

<3-3> Model of Mean Blood Pressure

A model of mean blood pressure is shown in Fig. 3. The model is obtained by synthesizing a submodel of the endocrine system and a submodel of the autonomic nervous system. The change of mean blood pressure is obtained as follows : Assuming that an output value of adrenaline, which is an input value of the cardio accelerator center, is $E_1(t)$, $E_1(t)$ is expressed as equation (3).

$$E_1(t) = G_5G_7G_8A(t)+G_1G_2\{ACTH(t)+G_4A(t)\} \quad (3)$$

ACTH(t) is the function of circadian variation of adrenocorticotrophic hormone, and A (t) is the function of circadian variation of angiotensin .

Assuming that the sum of the output value of noradrenaline and the output value of angiotensin , which is an input value of peripheral resistance, is $E_2(t)$, $E_2(t)$ is expressed as equation (4).

$$E_2(t) = (G_5G_7G_9+G_6)A(t) - G_1G_2\{ACTH(t)+G_4A(t)\} \quad (4)$$

Heart rate HR(t) is obtained from the change of the input value from the cardio accelerator center. HR(t) is assumed to be defined as equation (5).

$$HR(t) = HR_0+G_{10}G_{11}E_1(t) \quad (5)$$

Where HR_0 is heart rate in a steady state.

By multiplying heart rate by stroke volume, cardiac output per minute is obtained. It is difficult to measure stroke volume accurately. Stroke volume in a healthy subject is about 80 ml at rest in the supine position. When heart rate is high in a healthy subject, stroke volume hardly change. Stroke volume G_{12} is assumed to be 80 ml.

Cardiac output per minute MV(t) is expressed as equation (6).

$$MV(t) = G_{12}HR(t) = G_{12}\{HR_0+G_{10}G_{11}E_1(t)\} \quad (6)$$

MV(t), which is the change of cardiac output per minute caused by aldosteron is expressed as equation (7).

$$MV(t) = G_1G_3\{ACTH(t)+G_4A(t)\} \quad (7)$$

Assuming that peripheral resistance Z(t) is obtained by the sum of peripheral resistance Z_0 in a steady state and $G_{13}E_2(t)$, which is the change of peripheral resistance, Z(t) is expressed as equation (8).

$$Z(t) = Z_0+G_{13}E_2(t) \quad (8)$$

Mean blood pressure MBP(t) is obtained from MV(t), ΔMV(t) and Z(t). MBP(t) is expressed as equation (9).

$$MBP(t) = \{MV(t)+\Delta MV(t)\}Z(t) \quad (9)$$

4. MEASUREMENT AND SIMULATION OF HEART RATE AND MEAN BLOOD PRESSURE

<4-1> Measurement of Heart Rate and Mean Blood Pressure

Heart rate and mean blood pressure in 17 normal subjects and 17 essential hypertensive subjects were measured. Heart rate and mean blood pressure were measured under conditions of no exercise. The subjects slept continuously for one period each day.

Heart rate and mean blood pressure were measured for 48 hours and in a sampling interval of 30 minutes using ambulatory blood pressure monitoring appratuses. Mean blood pressure was measured by oscillometric method. An example of the results is shown in Fig. 4.

<4-2> Simulation of Heart rate and Mean Blood Pressure

Circadian variations of heart rate and mean blood pressure were simulated by equation (5) and equation (10) using the presented model. The parameters on the model are as follows : Let adrenal cortex gain G_1 and adrenal medulla gain G_7 be 1. Angiotensin gain G_4, which is input of the adrenal cortex, is set so output values of angiotensin are 1 maximum. Similarly, Angiotensin gain G_5, which is the input of the adrenal medulla, is set so the output values of angiotensin are 1 maximum.

Since stimulation to the adrenal cortex by adrenocorticotrophic hormone is relatively small compared with angiotensin , let A_a in equation (1) be 0.2. Let T_a in equation (1) be 24 hours. Assuming the hour of rising to be 8 a.m., let $_a$ in equation (1) be -2.1radians.

The ratio of adrenaline to noradrenaline in the adrenal gland is 9 [9]. Let adrenaline

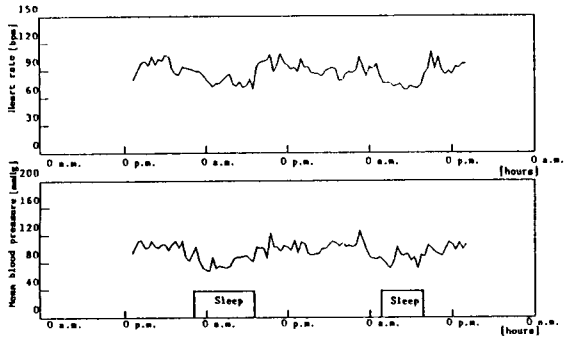

Fig.4 Measured result of heart rate and mean blood pressure.

G_1	Adrenal cortex gain	1.0	G_{10}	Cardio accelator center gain	1.5
G_2	Glucocorticoid gain	0.36	G_{11}	Heart rate gain	40
G_3	Aldosteron	100	G_{12}	Stroke volume	80 ml
G_4	Angiotensin II gain	8.33×10^{-3}	G_{13}	Peripheral resistance gain	0.2
G_5	Angiotensin II gain	8.33×10^{-3}	HR_0	Heart rate in steady state	60 bpm
G_6	Angiotensin II gain	0.025	Z_0	Peripheral resistance in steady state	13.2 mmHg/l/min
G_7	Adrenal medulla gain	1.0	A_0	Amplitude of circadian variation	0.2
G_8	Adrenaline gain	0.1	T_0	period	24 hours
G_9	Noradrenaline gain	1.0	φ_0	phase angle	-2.1 rad

Table 2 Parameters of the model in a normal subject.

gain G_8 be 0.1 and let noradrenaline gain G_9 be 1.0, respectively. Let glucocorticoid gain G_2 be 0.36.

Since angiotensin may bring on a four-fold increase of vasoconstriction [8] compared to noradrenaline, let angiotensin gain G_6 be 0.025. When heart rate HR_0 in a steady state is 60 beats per minute, cardio accelerator center gain G_{10} is 1.5, and heart rate gain G_{11} is 45.

Let stroke volume G_{12} in normal subjects be 80 ml. Stroke volume in essential hypertensive subjects decreases by 10 ml compared with normal subjects. Let stroke volume G_{12} in essential hypertensive subjects be 70 ml.

Volume of urine in a day is about 1000 ml. Let aldosteron gain G_3 be 100 so that changed values of cardiac output per minute by aldosteron are 150 ml maximum. Peripheral resistance Z_0 in steady state and peripheral resistance gain G_{13} are decided so that simulation results of mean blood pressure coincide with measured results of mean blood pressure. Let Z_0 in normal subjects be 12.2 mmHg/l/min. Let Z_0 in essential hypertensive subjects be 15.2 mmHg/l/min. Let peripheral resistance gain G_{13} be 0.2.

The simulation results of heart rate and mean blood pressure in a normal subject are shown in Fig. 5. Parameters on the model are shown in Table 2. The simulation results of heart rate and mean blood pressure in an essential hypertensive subjects are shown in Fig. 6. Parameters on the model are shown in Table 3.

The simulation results of heart rate and mean blood pressure were maximized in the morning and minimized in the evening. The simulation results coincided with the measured results.

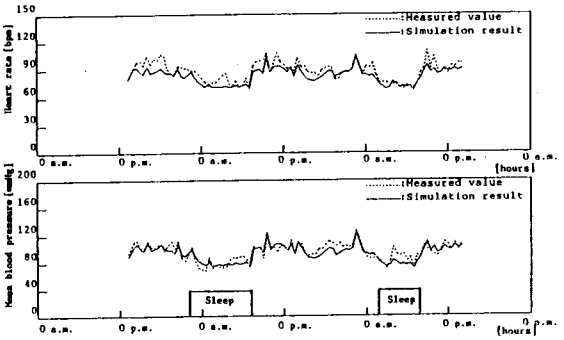

Fig.5 Comparison of measured result and simulation result of heart rate and mean blood pressure in a normal subject.

G_1	Adrenal cortex gain	1.0	G_{10}	Cardio accelator center gain	1.5
G_2	Glucocorticoid gain	0.36	G_{11}	Heart rate gain	40
G_3	Aldosteron	110	G_{12}	Stroke volume	70 ml
G_4	Angiotensin II gain	9.17 $\times 10^{-3}$	G_{13}	Peripheral resistance gain	0.24
G_5	Angiotensin II gain	9.17 $\times 10^{-3}$	HR_0	Heart rate in steady state	60 bpm
G_6	Angiotensin II gain	0.034	Z_0	Peripheral resistance in steady state	13.9 mmHg/ℓ/min
G_7	Adrenal medulla gain	1.0	A_m	Amplitude of circadian variation	0.2
G_8	Adrenaline gain	0.1	T_m	period	24 hours
G_9	Noradrenaline gain	1.0	φ_m	phase angle	-2.1 rad

Tabel 3 Parameters of the model in an essential hypertensive subject.

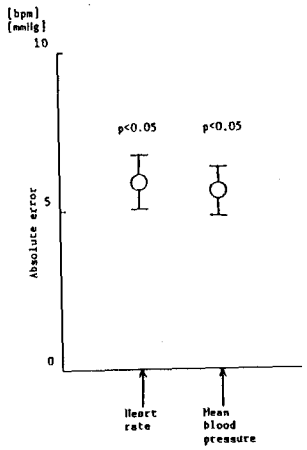

Fig.7 Standard deviations of absolute errors in measured values and simulation values of heart rate and mean blood pressure in normal subjects.

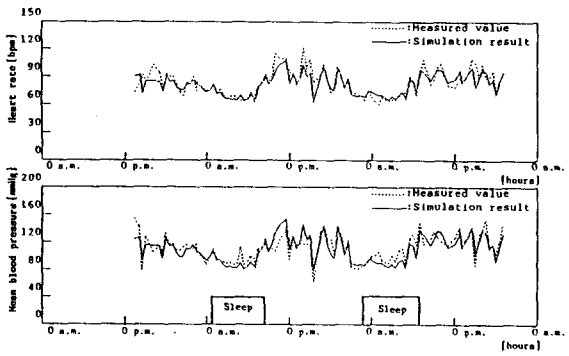

Fig.6

Fig.6 Comparison of measured result and simulation result of heart rate and mean blood pressure in an essential hypertensive subject.

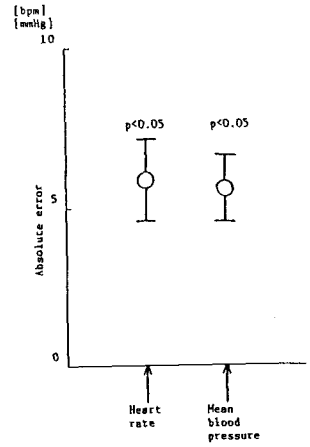

Fig.8 Standard deviations of absolute errors in measured values and simulation values of heart rate and mean blood pressure in essential hypertensive subjects.

5. EVALUATION OF THE PRESENTED MODEL AND DISCUSSION

Absolute errors between measured results and simulation results of heart rate and mean blood pressure were calculated to verify the presented model.

Absolute errors between the measured results and simulation results on heart rate and mean blood pressure in 17 normal subjects and 17 essential hypertensive subjects were calculated. The results in normal subjects and essential hypertensive subjects are shown in Fig. 7 and Fig. 8 respectively.

In normal subjects, absolute errors between heart rate and mean blood pressure were less than 7.0 beats per minute and less than 7.0 mmHg, respectively. In essential hypertensive subjects, absolute errors between heart rate and mean blood pressure were less than 7.0 beats per minute and less than 7.0 mmHg, respectively.

Absolute errors in heart rate were within 10 percent at 60 beats per minute at rest. Absolute errors in mean blood pressure were within 10 percent at 73 mmHg at rest. In normal subjects and essential hypertensive subjects, absolute errors between heart rate and mean blood pressure were less than 10 percent in heart rate at rest and in mean blood pressure at rest.

6. CONCLUSION

In this paper, a model of mean blood pressure employing the endocrine system and autonomic nervous system was presented. Heart rate and mean blood pressure in 17 normal subjects and 17 essential hypertensive subjects were measured and were simulated using the presented model. The results are summarized below.

(1) Measured results of heart rate and mean blood pressure coincided with simulation results.

(2) Absolute errors between measured results and simulation results of heart rate and mean blood pressure were calculated. The absolute errors were small.

Estimations of daily variations on heart rate and mean blood pressure in essential hypertensive subjects are possible by using the presented model. The model described in this study can be of much benefit used -in conjunction with medicine dosage- to predict heart rate and mean blood pressure in essential hypertensive patients.

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