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QUANTITATIVE EVALUATION OF THE BAROREFLEX SENSITIVITY OF AN ARTERY

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A b s t r a c t

There is no simple diagnostic method to measure the arterial behavior in the baroreflex system. Presently, we report the development of a method and associated hardware that enables the diagnosis of baroreflex sensitivity by measuring the responses of artery. In this system, the measurements are obtained by monitoring ECG and a pulse wave recorded from the radial artery. The arterial responses were measured in terms of the pulse wave velocity (PWV) calculated from the pulse wave transmission time (PTT) from the heart to the artery. Changes in the PTT in response to blood pressure changes were observed. A significant correlation was observed in the time sequence between blood pressure change and PTT change after calculating the delay time by cross-correlation. The slope of these parameter changes demonstrated the sensitivity of the baroreflex system of an artery. When tested clinically, decreased sensitivity of the baroreflex system in hypertensive patients was observed. This system may be useful when we consider the ideal treatment and follow-up of the patients with hypertension.

K e y w o r d s

Baroreflex sensitivity, Arterial baroreflex, Baroreceptor, Pulse wave transmission time, Pulse wave velocity

INTRODUCTION

Preventive medicine is a priority for most governments because of increasing medical and health care expenses (*1–7*). In Japan, the concept of metabolic syndrome has recently been identified to play an important role in the pathophysiology of many diseases (*3-7*). Hypertension, hyperlipidemia, diabetes mellitus, and obesity are important consequences of metabolic syndromes. Among these, hypertension is paramount when considering disruption of organ function (*8, 9*). Thus, prevention of hypertension is very important.

The baroreflex system is a key indicator of hypertensive pathophysiology (*10, 11*). When blood pressure (BP) increases, heart rate (HR) decreases, and there is peripheral arterial dilation (*12, 13*). By decreasing the cardiac output and peripheral arterial resistance, BP returns to normal. Hypertension is a concern in the young as well as the elderly (*14, 15*). Baroreflex sensitivity is reduced in younger hypertensive patients (*14-16*). However, currently there is no simple and sensitive diagnostic method to measure the arterial behavior in the baroreflex system.

Both responses of the HR and vasomotor components are important when we consider the precise quantitative diagnosis of the autonomic nervous system mediating the baroreflex system in the human body. However, no-one reported a method to evaluate the vasomotor components in the baroreflex system. No report describing the baroreflex sensitivity in vasomotor components can be cited when we check the Medline. Thus, we cannot evaluate the importance of the HR in baroreflex sensitivity, because we cannot evaluate the vasomotor components

Several investigators suggested the regional differentiation in autonomic responses in various human body areas. Thus, we cannot evaluate total response of the baroreflex system by only observing the HR. It may be a disadvantage if we cannot evaluate the precise quantification of the baroreflex system. Precise evaluation may be, of course, desirable, when we consider the ideal treatment and follow-up of patients with hypertension.

This study describes the development and clinical application of a new baroreflex diagnosis machine and offers a preliminary consideration of its clinical applicability.

MATERIAL AND METHODS

Diagnosis of arterial baroreflex sensitivity

Every medical student studies the baroreflex system as a typical example of homeostasis (*12-16*). When blood pressure increases, baroreceptors in the carotid arteries and aortic arch can sense. As shown in *Fig. 1*, the carotid sinus baroreceptors are innervated by the glossopharyngeal nerve, the aortic arch baroreceptors are innervated by the vagus nerve. With an information transmitting to the central nervous system, the HR lowers and arteries dilate by coupling sympathetic inhibition and parasympathetic activation. Thus, these responses restore the normal BP, because the sympathetic inhibition leads to a drop in peripheral resistance, while parasympathetic activation leads to a depressed heart rate and contractility.

In the conventional method, the baroreflex sensitivity was evaluated by measuring the HR response to the BP changes. The slope of the linear regression line demonstrated the sensitivity of the baroreflex system of the heart. While HR response in the baroreflex system can be monitored, no method currently exists to evaluate arterial baroreflex function, possibly because of the difficulty in evaluating vascular tone during wakefulness.

Recently, new methodologies like brachial ankle pulse wave velocity (baPWV) have been developed to evaluate human arterial stiffness (*17-20*). These methodologies non-invasively evaluate arterial wall stiffness using the pulse waveform of the brachial and ankle arteries. These methodologies are based on the premise that pulse wave velocity (PWV) is correlated with arterial wall stiffness. Thus, PWV increases when the arterial wall becomes harder and decreases when the arterial wall softens.

In the baroreflex system, the arterial wall softens in response to an increase in BP, thereby decreasing the vascular resistance as shown in *Figure 1*. BP will return to normal because of the decrease in resistance. The softness of the arterial wall can be measured by PWV.

The PWV value could possibly be used to quantitatively measure the baroreflex sensitivity of the arterial wall. PWV can be calculated from the pulse wave transmission time (PTT) and distance (*Fig. 2*). Thus, measurements of PTT and BP permit an evaluation of arterial baroreflex response. Time was calculated from R wave in ECG and up-sloping point of pressure waveform.

Animal experiments

To evaluate the autonomic responses of the PTT or PWV, chronic animal experiments were carried out using healthy adult goats. All experiments were approved by the Ethical Committee of the Institute of Development, Aging and Cancer, Tohoku University. Under anesthesia, the chest cavity was opened in the fourth intercostal space. Implants included an electromagnetic flow meter, electrodes for electrocardiogram (ECG), a catheter-tip pressure sensor inserted into the femoral artery, and a fluid-filled catheter inserted into the left ventricle. After the chest was closed, the goats were moved to their cages. Measurements were taken when the goats were conscious in the chronic stage. Since PWV value can be used to quantitatively measure the baroreflex sensitivity of the arterial wall, PWV is calculated from the pulse wave transmission time (PTT) and distance. Time was calculated from R wave in ECG and up-sloping point of pressure waveform.

After the termination of the effect of anesthesia, we evaluated the hemodynamic responses to the sudden alteration of the hemodynamic parameters with drug administration like methoxamine,1-adrenoceptor agonist, for the quantitative diagnosis of the baroreflex system.

Measurement equipment and analysis

PTT and PWV were easily measured by monitoring ECG and pulse wave. *Fig. 3* shows the equipment used for the measurement. The newly developed system used only an ECG and a pulse wave recorded from the radial artery. These time series were inputted into a personal computer, and analyzed quantitatively using a customized software.

The time series for HR, BP, and PTT are depicted in *Fig.4*. HR was calculated from the reciprocal of the inter-R-wave interval of the ECG signal. PTT was defined as the time interval from the peak of the R-wave to the point at which the pulse wave signal began to increase. HR and PTT were interpolated by cubic spine functions to continuous-time functions, and were resampled every 0.5 s.

Fig. 5 displays an example of the cross-correlation function between the systolic BP and PTT. The strongest correlation was observed approximately 6.0 s later. Thus, a band-pass filter was used in the analyses. Each data point was filtered through a band-pass filter with a bandwidth between 0.08-0.1 Hz to extract the Mayer wave component.

Fig. 6 displays an example of the correlation between the systolic BP and PTT. PTT was plotted after 6.0 s. A significant correlation was evident in the time sequence between BP change and PTT change after calculating the delay time by cross-correlation. The slope of these parameter changes was easily obtained, and it demonstrated the sensitivity of the baroreflex system of an artery.

The utility of this system for the quantitative diagnosis of the baroreflex sensitivity of an artery was recognized by the patent application.

Clinical evaluation

The arterial responses were measured in terms of the PWV calculated from the PTT from the heart to an artery. In this system, the HR change corresponding to the BP change in time series sequence was observed. Delay time was measured by the cross-correlation function. The slope of the changes in BP and HR indicates the sensitivity of the baroreflex system of the heart. Furthermore, this system could also measure the sensitivity of the baroreflex system of an artery. Thus, after obtaining the ethical committee allowance of the Tohoku University Graduate school of Medicine and related hospitals, clinical application was started. Nine healthy male volunteers and twenty patients with essential hypertension (10 males, 10 females) were evaluated in this study. In the lying position, radial artery waveform was evaluated with a tonometry sensor (Jentow 7700, Colin, Tokyo) and ECG was measured by a physiological amplifier (ECG100C; BIOPAC System Inc.). These signals were converted to digital signals by a 16-bit A/D converter (MP100; BIOPAC System Inc.) and stored in a personal computer (Vaio, Sony, Tokyo) every 1 ms. Beat-to-beat variables of R-wave interval (RRI [ms]) and systolic blood pressure (SBP [mmHg]) were calculated from the ECG and continuous arterial blood pressure signals, respectively.

This is the first feasibility study, so the examples were shown in the results.

RESULTS

Animal experiments

After an intravenous injection with methoxamine, 1-adrenoceptor agonist, BP suddenly increased (*Fig. 7*). HR was reduced in response to the increase in systolic pressure, and PTT increased in response to the BP change. Prolongation of the PTT indicated softening of the artery. Therefore, PTT and PWV were thought to be indicative of the autonomic response of an artery.

To demonstrate the autonomic nervous control of the HR and PTT, the autonomic nerves were blocked using atropine and propranolol (*21–22*). During this blockage, HR did not respond to the BP change; however, PTT showed marginal decrease in response to the increase in systolic pressure (*Fig. 8*). This small decrease of the latter might have been due to hardening of the artery caused by methoxamine.

The results are consistent with HR and PTT, being indicative of the autonomic response to BP changes in the baroreflex system.

Clinical evaluation

Fig. 9 displays an example of a patient report. Upper tracings of HR, BP and PTT are shown, and their spectral analysis data are displayed on the left. On the lower right-hand part of the report, cardiac and arterial baroreflex sensitivity is provided along with an analysis of the cross-correlation function. In this patient, the calculated standardized baroreflex sensitivity of the heart was 0.28 and baroreflex sensitivity of the artery was 0.72.

Clinical research of our study has begun after obtaining ethical committee allowance. So far, the results have shown that our system can successfully detect decreased sensitivity of the baroreflex system in hypertensive patients. *Fig. 10* showed a typical example of data showing arterial baroreflex sensitivity. No correlation was observed between the BP change and PTT change. Thus, in some patients with essential hypertension, arterial baroreflex sensitivity was significantly reduced.

Furthermore, in some patients improvement of arterial baroreflex sensitivity was observed, as shown in *Fig. 11*.

DISCUSSION

The concept of metabolic syndrome has become an important issue in Japan, as well as in other countries. Within the concept, hypertension is one of the most important factors when we consider the organ damage. Thus, preventive medicine has become important and the baroreflex system is an important issue when we consider the pathogenesis of the hypertension.

The results of animal experiments suggested that we can evaluate the autonomic function of the arterial tree using information on PTT and PWV. PTT was mediated by the autonomic nervous system, so PTT change was blocked after autonomic blockades. Yes, we can evaluate the autonomic nerve control of an artery using the information on PTT.

After the evaluation of animal experiments, the clinical application was started after obtaining ethical committee allowance. Our recent results suggested that at least in some patients with essential hypertension, arterial baroreflex sensitivity was reduced. Furthermore, arterial baroreflex sensitivity was improved with drug administration in some patients. These results suggest that we may be able to monitor the pathophysiological condition of patients with hypertension.

We have now been analyzing the various data of patients with hypertension by gathering data from related hospitals. Further examination will be needed using more cases. This new method may be useful to follow up patients with hypertension.

CONCLUSION

A new method for evaluation of the arterial baroreflex sensitivity was developed and clinical application started after the feasibility study using animal experiments. Our results suggested that arterial baroreflex sensitivity was reduced at least in some patients with essential hypertension. Furthermore, arterial baroreflex sensitivity was improved with treatments. These results suggest that this new method may be useful to follow up patients with hypertension.

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REFERENCES

1. *Clements D*. Incentives for preventive medicine in general practice. Lancet 1989 Apr 22; 1(8643): 906.
2. *Scutchfield FD, de Moor C.* Preventive attitudes, beliefs, and practices of physicians in fee-for-service and health maintenance organization settings.
3. *Funahashi T, Matsuzawa Y*. Metabolic syndrome: clinical concept and molecular basis. Ann Med 2007 Jul 20; 1–13 [Epub ahead of print].
4. *Yatsuya H.* Pathophysiologic mechanisms of obesity and related metabolic disorders: an epidemiologic study using questionnaire and serologic biomarkers. J Epidemiol 2007; 17(5): 141–146.
5. *Takahashi K, Bokura H, Kobayashi S, Iijima K, Nagai A, Yamaguchi S*. Metabolic syndrome increases the risk of ischemic stroke in women. Intern Med 2007; 46(10): 643–8. Epub 2007 May 24.
6. *Okamura T, Nakamura K, Kanda H, et al*. Health Promotion Research Committee, Shiga National Health Insurance Organizations. Effect of combined cardiovascular risk factors on individual and population medical expenditures: a 10-year cohort study of national health insurance in a Japanese population. Circ J 2007; 71(6): 807–813.
7. *Ninomiya T, Kubo M, Doi Y, et al*. Impact of metabolic syndrome on the development of cardiovascular disease in a general Japanese population: the Hisayama study. Stroke 2007; 38(7): 2063–9. Epub 2007 May 24.
8. *Ishikawa S, Shibano Y, Asai Y, Kario K, Kayaba K, Kajii E*. Blood pressure categories and cardiovascular risk factors in Japan: the Jichi Medical School (JMS) Cohort Study. Hypertens Res 2007; 30(7): 643–649.
9. *Uzu T, Kimura G, Yamauchi A, et al*. Enhanced sodium sensitivity and disturbed circadian rhythm of blood pressure in essential hypertension. J Hypertens 2006; 24(8): 1627–1632.
10. *Straznicky NE, Lambert EA, Lambert GW, Masuo K, Esler MD, Nestel PJ*. Effects of dietary weight loss on sympathetic activity and cardiac risk factors associated with the metabolic syndrome. J Clin Endocrinol Metab 2005; 90(11): 5998–6005. Epub 2005 Aug 9.
11. *Grassi G, Dell'Oro R, Quarti-Trevano F, et al*. Neuroadrenergic and reflex abnormalities in patients with metabolic syndrome. Diabetologia 2005; 48(7): 1359–65. Epub 2005 Jun 3.
12. *Chen HI.* Mechanism of alteration in baroreflex cardiovascular responses due to volume loading. Jpn J Physiol 1978; 28(6): 749–756.
13. *Goldstein DS, Harris AH, Brady JV.* Baroreflex sensitivity during operant blood pressure conditioning. Biofeedback Self Regul 1977; 2(2): 127–138.
14. *Krontoradova K, Honzikova N, Fiser B, et al.* Overweight and decreased baroreflex sensitivity as independent risk factors for hypertension in children, adolescents, and young adults. Physiol Res 2007; May 30 [Epub ahead of print].
15. *Fu Q, Townsend NE, Shiller SM, et al.* Intermittent hypobaric hypoxia exposure does not cause sustained alterations in autonomic control of blood pressure in young athletes. Am J Physiol Regul Integr Comp Physiol 2007; 292(5): R1977–84. Epub 2007 Jan 4.
16. *Honzikova N, Novakova Z, Zavodna E, et al*. Baroreflex sensitivity in children, adolescents, and young adults with essential and white-coat hypertension. Klin Padiatr 2006; 218(4): 237–242.
17. *Yambe T, Kovalev YA, Milyagina IA, et al.* A Japanese-Russian collaborative study on aging and atherosclerosis. Biomed Pharmacother 2004; 58 (Suppl 1): S91–94.
18. *Yamashina A, Tomiyama H, Arai T, et al*. Nomogram of the relation of brachial-ankle pulse wave velocity with blood pressure. Hypertens Res 2003; 26(10): 801–806.
19. *Yambe T, Meng X, Hou X, et al.* Cardio-ankle vascular index (CAVI) for the monitoring of the atherosclerosis after heart transplantation. Biomed Pharmacother 2005; 59 (Suppl 1): S177–179.
20. *Yambe T, Yoshizawa M, Saijo Y, et al.* Brachio-ankle pulse wave velocity and cardio-ankle vascular index (CAVI). Biomed Pharmacother 2004; 58 (Suppl 1): S95–98.
21. *Kumagai H, Suzuki H, Ryuzaki M, Matsukawa S, Saruta T*. Baroreflex control of renal sympathetic nerve activity is potentiated at early phase of two-kidney, one-clip Goldblatt hypertension in conscious rabbits. Circ Res 1990; 67(6): 1309–1322.
22. *Jose AD, Taylor RR.* Autonomic blockade by propranolol and atropine to study intrinsic myocardial function in man. J Clin Invest 1969; 48(11): 2019–2031.

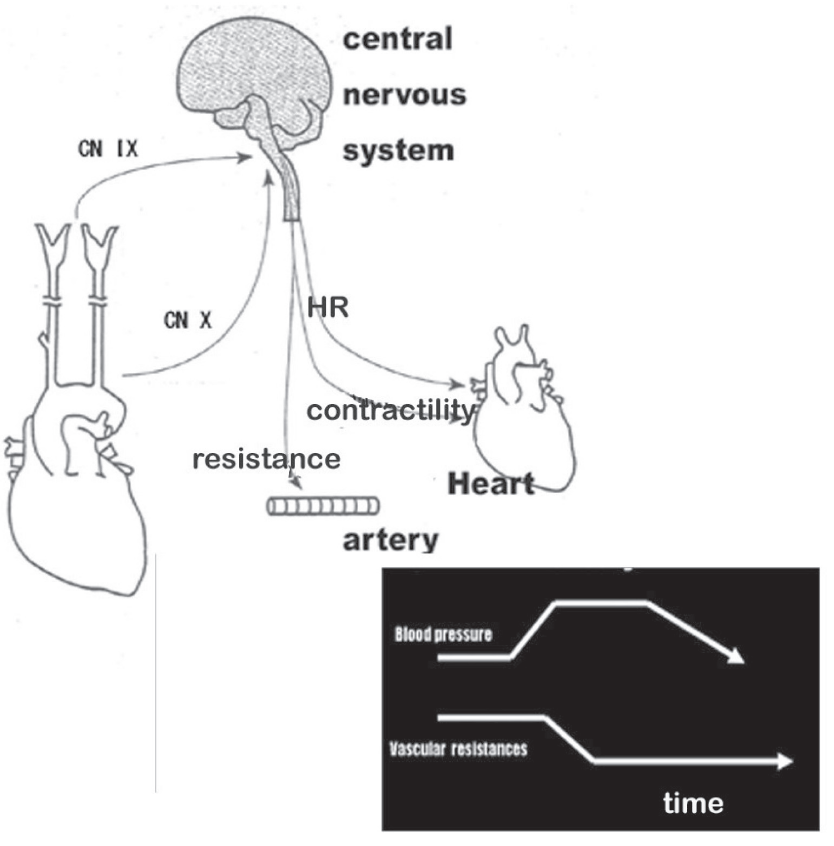

Fig. 1

Schematic diagram of the baroreflex system. The carotid sinus baroreceptors are innervated by the glossopharyngeal nerve (CN IX); the aortic arch baroreceptors are innervated by the vagus nerve (CN X). When baroreceptors are activated by increased blood pressure, the nucleus of the solitary tract (NTS) activates the caudal ventrolateral medulla (CVLM) and inhibits the rostral ventrolateral medulla (RVLM), thus inhibiting the sympathetic branch of the autonomic nervous system and activating the parasympathetic nervous system, resulting in the reduction of HR, ventricular contractility, and dilatation of the artery. As the regulating results, peripheral vascular resistances are decreased in response to the blood pressure increase in time series data.

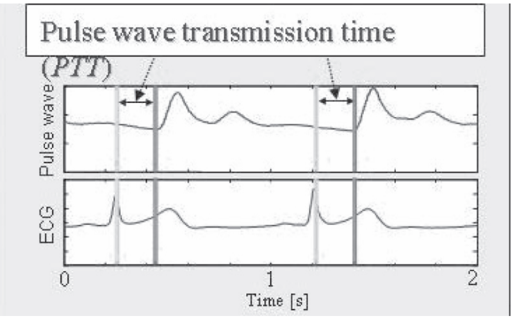

Fig. 2
Schematic diagram to explain the pulse wave velocity (PWV). After the left ventricular contraction, the pulse was moved from the ascending aorta to the peripheral artery. Thus, we can evaluate the PWV from time and distance. Time was calculated from R wave in ECG and up-sloping point of the pressure waveform.

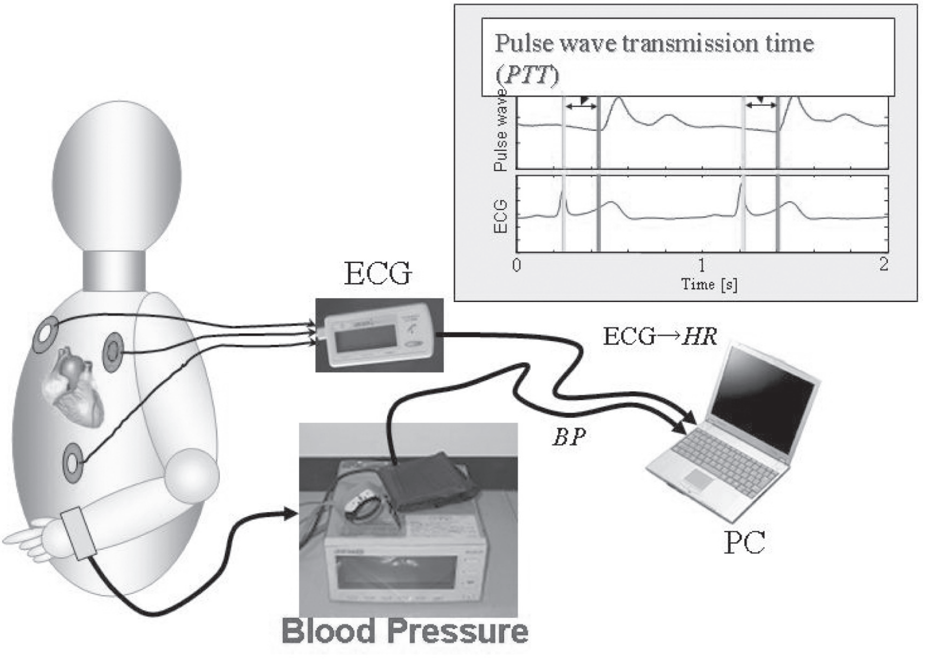

Fig. 3
A schematic illustration of the measurement equipment. By the use of the ECG and radial artery waveform, we can calculate the pulse wave transmission time from R wave in ECG and rising point of the radial arterial pressure waveform.

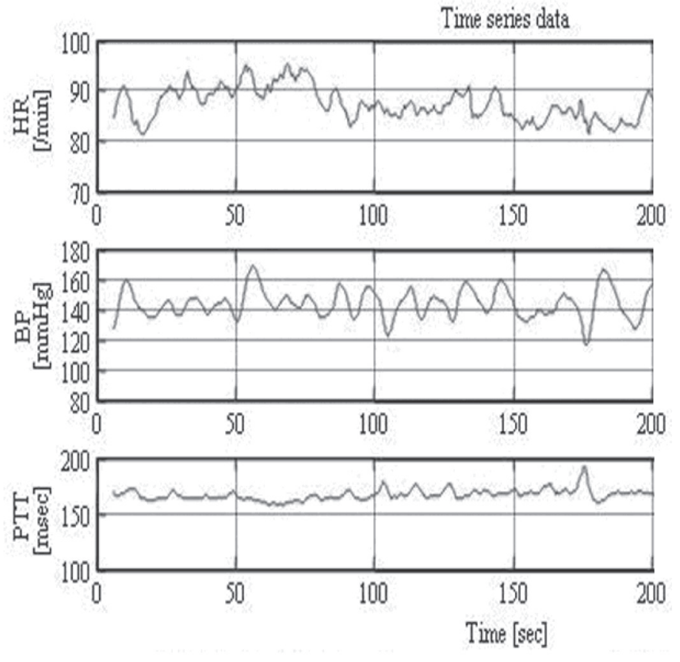

Fig. 4
Time series data of the HR, BP and PTT of a healthy volunteer in resting condition. Fluctuation in time series data was observed.

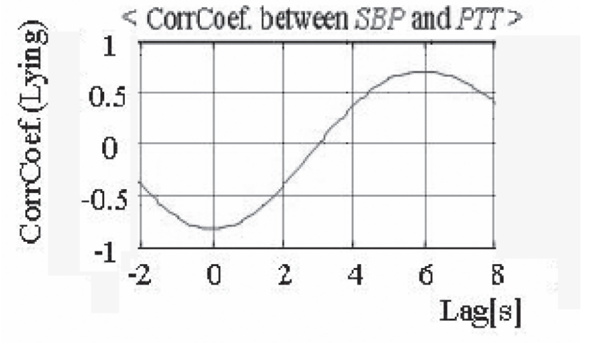

Fig. 5
An example of the cross-correlation function between systolic BP and PTT. The largest correlation was observed after 6.0 seconds.

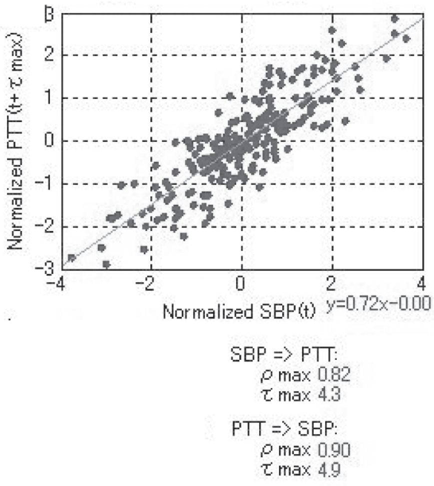

Fig. 6
An example of the correlation between the normalized systolic BP and normalized PTT in a patient. A significant correlation was observed, and the slope, suggesting the baroreflex sensitivity of the arterial tree, was calculated from the regression line from the least square method.

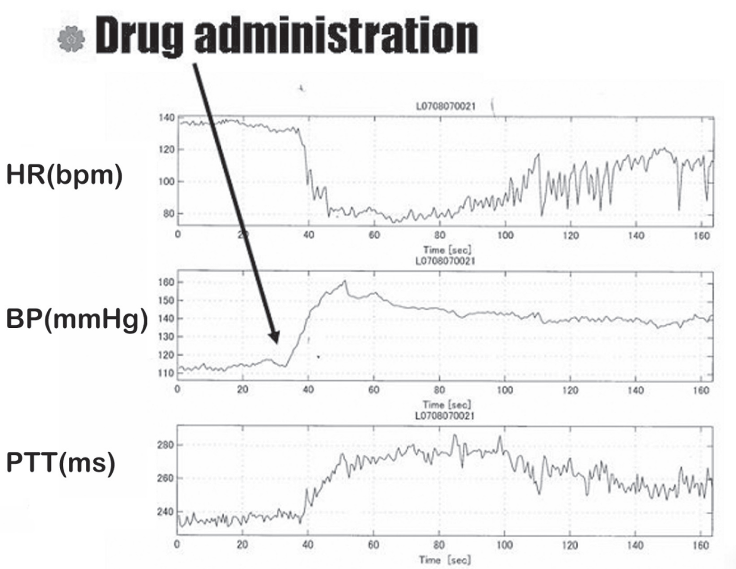

Fig. 7
Time series data of heart rate (HR), systolic blood pressure (BP) and pulse wave transmission time (PTT) in a healthy and conscious adult goat in response to suddenly increased BP by drug administration with methoxamine sulfate. HR was reduced in response to BP rise. PTT was increased in response to BP rise.

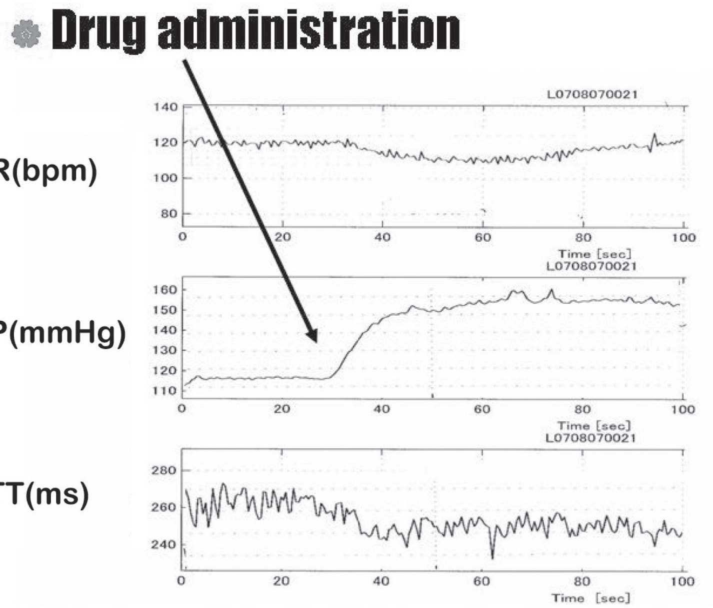

Fig. 8

Time series data of HR, systolic BP, and PTT in a healthy and conscious adult goat after complete blockage of an autonomic nervous system using atropine and propranolol. BP was increased by drug administration with methoxamine sulfate; however, the responses of HR and PTT were diminished.

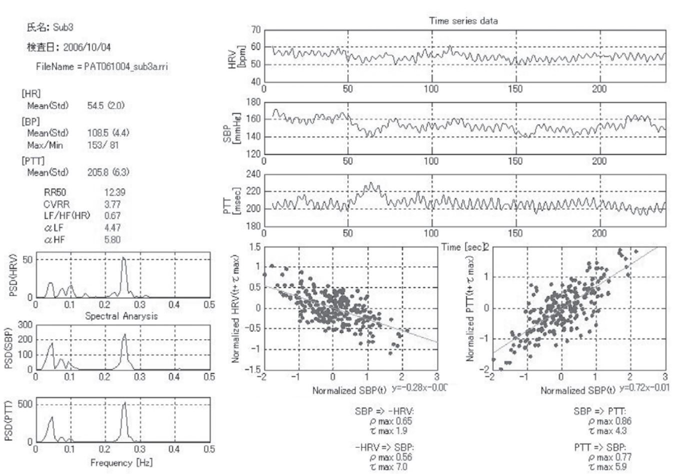

Fig. 9

An example of a patient report from the baroreflex sensitivity diagnosis machine. Time series data of HR, BR, and PTT were shown upper right. Spectral analyzing results of HR, BP and PTT were reported lower left. Baroreflex sensitivity regression lines were shown lower right in this report.

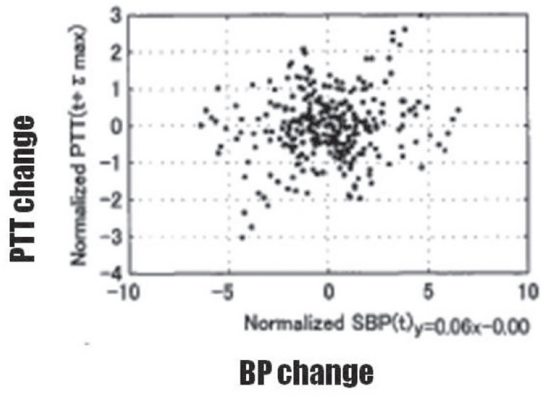

Fig. 10
An example of the correlation between the normalized systolic BP and normalized PTT in a patient with hypertension. No correlation was observed, suggesting the disturbance of the arterial baroreflex system.

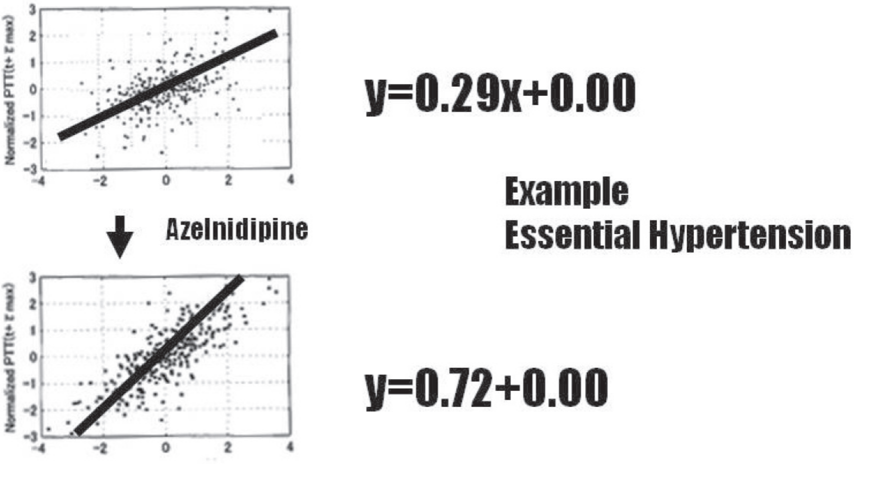

Fig. 11
An example of the improvement of arterial baroreflex sensitivity after the calcium blockade treatment using Azelnidipine, a Calcium blockade agent.