31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Development of new quantitative diagnosis machine to evaluate the Baroreflex sensitivity of an artery for patients with hypertension

Tomoyuki Yambe, Norihiro Sugita, and Makoto Yoshizawa, *Member, IEEE*

Abstract—Text book in all medical school showed that the baroreflex system is one of the most important regulatory systems. When blood pressure increases, heart rate decrease and an artery is dilated with the baroreflex system. By decrease of cardiac output and arterial resistances, blood pressure returns to the normal value. However, there is no diagnostic method, which can measure the sensitivity of a baroreflex system of the artery by the simple methodology. We had challenged invention of the new machine, which could diagnose the sensitivity of the baroreflex system of not only a heart, but also an artery. In this system, the measurement sections are only an electrocardiography (ECG) and peripheral pulse wave. These time series is inputted into a personal computer system, and analyzed quantitatively. Responses of the artery were measured with pulse wave velocity (PWV) calculated from pulse wave transmission time from heart to an artery. In this system, the heart rate change corresponding to the blood-pressure change in time series sequence is observed. Delay time was measured by the cross correlation function. Slope of the blood pressure (BP) change and heart rate (HR) change showed the sensitivity of the baroreflex system of heart. Furthermore, this system can measure the sensitivity of the baroreflex system of an artery. Change of PWV in response to the BP change was observed. We found that significant correlation was observed in the time sequence between BP change and PWV change after delay time calculated from cross correlation. Clinical research was started through allowance of the Ethics Committee. Decreased sensibility in the hypertensive patient's baroreflex system was observed as a result of the clinical research. Furthermore, alteration of the baroreflex sensitivity before and after the drug administration was evaluated. For example, Azelnidipine, Calcium antagonists improved the baroreflex sensitivity of the artery in several cases. This system may be useful for the follow up of the hypertensive patients

I. Introduction

ONE of the most important key words for the every government is the Preventive medicine, because medical fee is increasing more and more in every country (1-7). In Japan, the concept of the Metabolic syndrome had become one of the most important patho-physiological factors (3-7). Hypertension, hyper-lipidemia, diabetes mellitus, and obesity were the important factors of the Metabolic syndrome. Among these factors, hypertension is one of the most important factors, when we consider the disturbing organ function (8, 9). So, prevention of the hypertension is very important.

A lot of reports studying the hypertensive patho-physiology noted that the baroreflex system is one of the most important factors (10, 11). When blood pressure increases, heart rate decrease and an artery is dilated with the baroreflex system in the normal human body (12, 13). By decrease of cardiac output and peripheral arterial resistances, blood pressure returns to the normal value. However, there is no diagnostic method, which can measure the sensitivity of a baroreflex system of the artery by the simple methodology.

Hypertension in younger people is important in preventive medicine (14, 15). Several investigators noted that baroreflex sensitivity was reduced in the younger hypertension patients (14-16). Baroreflex sensitivity was so important, however, there was no methodology to measure the baroreflex sensitivity of an artery.

Invention of the new machine, which could diagnose the sensitivity of the baroreflex system of not only a heart, but also an artery is tried in this study. This paper described the development and clinical application of the new baroreflex diagnose machine and consideration was added to the results

II. DIAGNOSIS OF THE BAROREFLEX SENSITIVITY OF AN ARTERY

As the typical example of the Homeostasis in the textbook of every medical school, students must learn the Baroreflex system (12-16). When the blood pressure was increased, baroreceptors in the carotid arteries and aortic arch sensed the increase of the baroreflex system. When this information was conducted to the central nervous system, heart rate was responded to reduce and arteries were dilated. So, blood pressure was returned to the normal value.

Sensitivity of the baroreflex sensitivity was evaluated by the heart rate (HR) responses to the blood pressure changes. Slope of the linear regression line showed the sensitivity of the baroreflex system for heart.

There was method evaluating the response of the heart rate in baroreflex system, however, there was no method to evaluate the baroreflex function of an artery. It may be because of the difficulty to evaluate the vascular tone in human body in the awaking condition.

Recently new diagnosing method to evaluate the arterial stiffness in human body for the diagnosis of the

Manuscript received April 8, 2009. This work was partly supported by support of Tohoku University Global COE Program Global Nano-Biomedical Engineering Education and Research Network Centre .

T.Yambe , M.Yoshizawa, N.Sugita are with the Tohoku University, 4-1 Seryo-machi, Aoba-ku, Sendai 980-8575, Japan
(e-mail: yambe@idac.tohoku.ac.jp)

atherosclerosis was developed. Brachial ankle pulse wave velocity (baPWV) and the Cardio Ankle Vascular Index (CAVI) were the new methodology to evaluate the arterial stiffness in human body (17-20). These methodologies could evaluate the arterial wall stiffness with non invasive measurement using pulse waveform of the brachial artery and ankle artery. These methodologies were based on the theory that pulse wave velocity (PWV) was correlated with the arterial wall stiffness. PWV will be increased when arterial wall become harder. PWV will be decreased when arterial wall become softer.

In the baroreflex system, an artery will become soft by reflection in response to a blood-pressure rise as we shown in Fig.1. Vascular resistance will be decreased as an artery becomes soft. Blood pressure will be returned to a normal value, because of the decrease in resistance. The softness of an artery can be measured by PWV and CAVI.

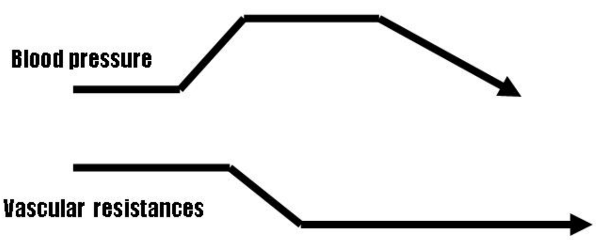

Fig. 1. Schematic concept of the time series data of the responses of the baroreflex system of the vascular resistance

If the information of the PWV is used for the baroreflex responses, we can measure the baroreflex sensitivity of the arterial wall, quantitatively. Pulse wave velocity was calculated from the pulse wave transmission time (PTT) and distance as we shown in fig.2. PWV was calculated from the time and distance.

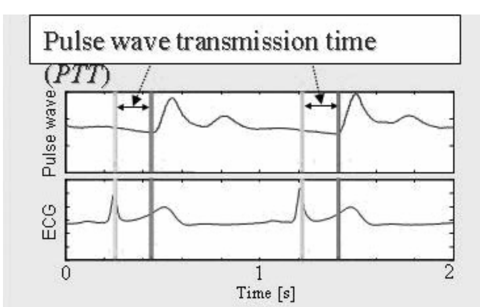

Fig. 2. Time series data of ECG, Pulse wave and Pulse wave transmission time (PTT)

So, if we measure the PTT and blood pressure, we can evaluate the baroreflex responses of an artery.

III. ANIMAL EXPERIMENTS

Does PWV show autonomic nerve's reflection?

To evaluate the autonomic response of the PTT or PWV, chronic animal experiments were carried out using healthy adult goats. Healthy adult goats, which had the almost same weight as the average Japanese people, were used in these experimental series after animal experiments ethical committee allowance of Institute of Development, Aging and Cancer in Tohoku University. After anesthesia inhalation, chest cavity was opened in the fourth inter-costal space. Electromagnetic flow meter, Electrodes for ECG, catheter tip pressure sensor inserted into the femoral artery, and fluid filled catheter inserted into the left ventricle were implanted. After the chest was closed, the goats were moved to the cage. Measurements were performed in the awaking condition in the chronic stage.

By the intravenous injection of methoxamine, blood pressure was suddenly increased and Heart rate was reduced responsively to the systolic pressure rise. And PTT was increased in response to BP change. Prolongation of the PTT showed the softening of an artery. So, PTT and PWV were thought to be showed the autonomic response of an artery.

Was this phenomenon based on autonomic nerves system?

To evaluate the autonomic nervous control of the HR and PTT, pharmacological autonomic nerve blockade was tried in this study using atropine sulfate and propranolol. After the blockade of the autonomic nerve, HR did not response to the blood pressure change. PTT did not response to the systolic pressure rise. PTT showed a little decrease. This small decrease may show the hardening of an artery by the methoxamine.

As the results, HR and PTT showed the autonomic response to the blood pressure changes through the baroreflex system.

IV. MEASUREMENT EQUIPMENT AND ANALYSIS

PTT and PWV were easily measured with ECG and pulse wave as we shown in Fig.3.

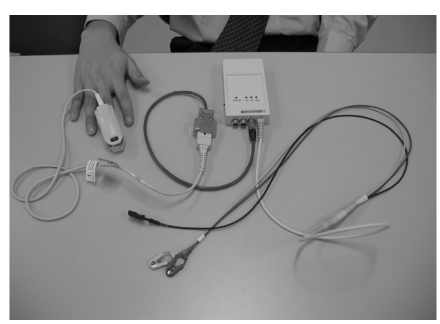

Fig.3 Photograph of the measurement equipment.

In newly developed system, the measurement sections are only an electrocardiogram (ECG) and a peripheral pulse wave. These time series data is inputted into a personal computer system, and is analyzed quantitatively. 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 ECG, R-wave, to the point at which the pulse wave signal begins to rise. HR and PTT were interpolated by cubic spline functions to be continuous-time functions, and were re-sampled every t = 0.5 s. Cross correlation function between the systolic BP and PTT was calculated. As the results, strongest correlation was observed almost 6 seconds after. Thus, Band pass filter was used in the analysis. Each data point was then filtered through a band-pass filter with a bandwidth between 0.08 Hz and 0.1 Hz to extract the Mayer wave component.

Fig.4 showed an example of the correlation between the systolic BP and PTT. PTT was plotted 6.0 seconds after according to the analyzing results from the cross correlation function. We found that significant correlation was observed in the time sequence between BP change and PTT change after delay time calculated from cross correlation. Slope of the BP change and PWV change was easily obtained and showed the sensitivity of the baroreflex system of an artery. This new invention was useful system for the quantitative diagnosis of the baroreflex sensitivity of an artery, so we applied the patent.

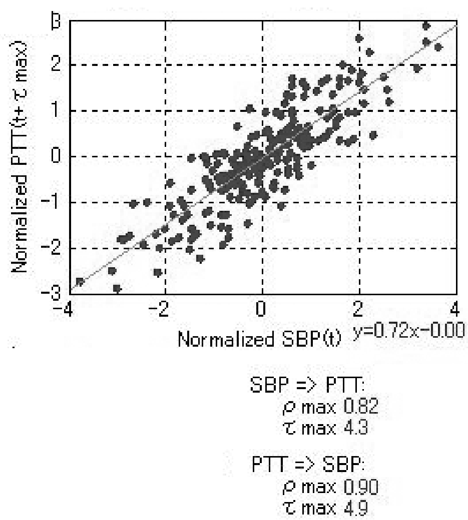

Fig.4 An example of the correlation between the normalized systolic blood pressure and normalized PTT in human body

Responses of the artery with baroreflex system were measured with pulse wave velocity calculated from PTT from heart to an artery. In this system, the heart rate change corresponding to the blood-pressure change in time series sequence is observed. Delay time was measured by the cross correlation function. Slope of the BP change and HR change showed the sensitivity of the baroreflex system of heart. Furthermore, this system can measure the sensitivity of the baroreflex system of an artery.

Fig.5 showed an example of the patient report. From upper tracing HR, BP and PTT were described. In the left sides, analyzing results of the spectral analysis of the HR, BP and PTT were shown. On the lower parts of the right sides in this patient report, baroreflex sensitivity of the heart and artery were shown with the analyzing results of the cross correlation function.

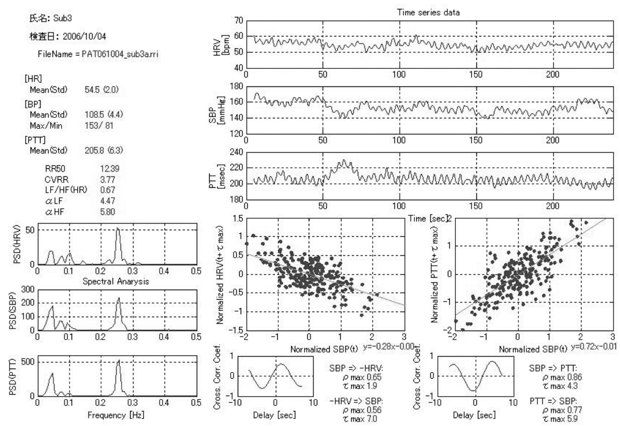

Fig.5 Patients reports from baroreflex sensitivity diagnosis machine.

In this patient, calculated result of the standardized baroreflex sensitivity of the heart was 0.20 and baroreflex sensitivity of an artery was 0.72.

V. CLINICAL APPLICATION

Clinical research was started through allowance of the Ethics Committee of the Tohoku University Hospital and related hospitals of our Institutes. As the results, decreased sensibility in the hypertensive patient's baroreflex system was observed as a result of the clinical research in the hospitals.

Furthermore, alteration of the baroreflex sensitivity before and after the drug administration was evaluated. For example, Azelnidipine, Calcium antagonists improved the baroreflex sensitivity of the artery.

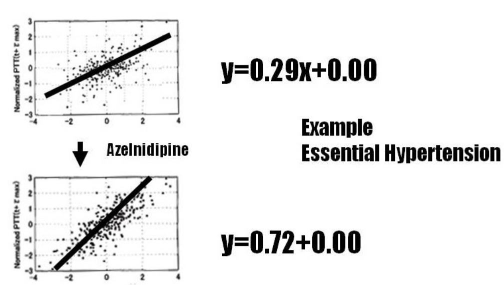

Fig. 6 An example of the improvement of the baroreflex sensitivity of an artery before and after the treatment with Ca antagonists

In the 7 cases, which we could evaluate the reliable calculating results, baroreflex sensitivity of an artery was improved in 6 cases before and after the Azelnidipine administration. And the baroreflex sensitivity of an artery was decreased in one case.

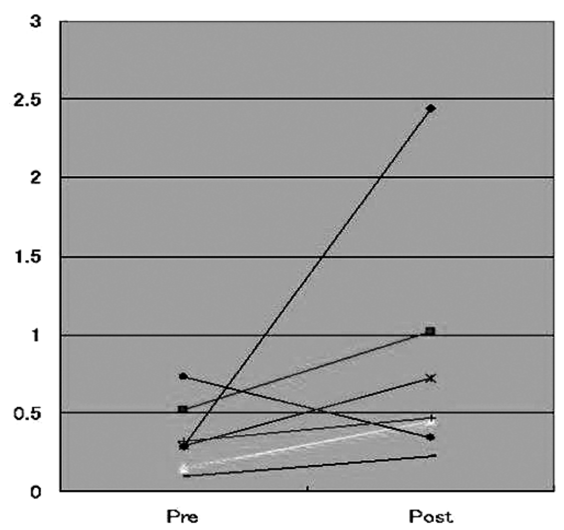

Fig.7 Summary of the baroreflex sensitivity of an artery in seven cases with hypertension

Though, there was no statistical significance in the quantitative baroreflex sensitivity of an artery before and after the administration, we might not to be able to ignore the therapeutic effect of Calcium antagonists on baroreflex system when we consider the therapeutic mechanisms.

VI. CONCLUSION

Further examination will be needed to compare the effect of anti hypertensive drugs upon baroreflex sensitivity of the heart and artery. This new method may be useful for the follow up of the patients with hypertension

ACKNOWLEDGMENT

This work was partly supported by support of Tohoku University Global COE Program "Global Nano-Biomedical Engineering Education and Research Network Centre". And Research Grant from Mitsui Sumitomo Insurance Welfare Foundation, Nakatani Electronic Measuring Technology Association of Japan, Japan Epilepsy Research Foundation, Naito Foundation

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

[4] Yatsuya H. Pathophysiologic mechanisms of obesity and related metabolic disorders: an epidemiologic study using questionnaire and serologic biomarkers.J Epidemiol. 2007 Sep;17(5):141-6.

[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, Hayakawa T, Hozawa A, Murakami Y, Kadowaki T, Kita Y, Okayama A, Ueshima H; 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 Jun;71(6):807-13.

[7] Ninomiya T, Kubo M, Doi Y, Yonemoto K, Tanizaki Y, Rahman M, Arima H, Tsuryuya K, Iida M, Kiyohara Y. Impact of metabolic syndrome on the development of cardiovascular disease in a general Japanese population: the Hisayama study. Stroke. 2007 Jul;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 Jul;30(7):643-9.

[9] [9] Uzu T, Kimura G, Yamauchi A, Kanasaki M, Isshiki K, Araki S, Sugiomoto T, Nishio Y, Maegawa H, Koya D, Haneda M, Kashiwagi A. Enhanced sodium sensitivity and disturbed circadian rhythm of blood pressure in essential hypertension. J Hypertens. 2006 Aug;24(8):1627-32.

[10] [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 Nov;90(11):5998-6005. Epub 2005 Aug 9.

[11] Grassi G, Dell'Oro R, Quarti-Trevano F, Scopelliti F, Seravalle G, Paleari F, Gamba PL, Mancia G. Neuroadrenergic and reflex abnormalities in patients with metabolic syndrome. Diabetologia. 2005 Jul;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):749-56.

[13] Goldstein DS, Harris AH, Brady JV. Baroreflex sensitivity during operant blood pressure conditioning. Biofeedback Self Regul. 1977 Jun;2(2):127-38.

[14] Krontoradova K, Honzikova N, Fiser B, Novakova Z, Zavodna E, Hrstkova H, Honzik P. 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, Martini ER, Okazaki K, Shibata S, Truijens MJ, Rodriguez FA, Gore CJ, Stray-Gundersen J, Levine BD. 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 May;292(5):R1977-84. Epub 2007 Jan 4.

[16] Honzikova N, Novakova Z, Zavodna E, Paderova J, Lokaj P, Fiser B, Balcarkova P, Hrstkova H. Baroreflex sensitivity in children, adolescents, and young adults with essential and white-coat hypertension. Klin Padiatr. 2006 Jul-Aug;218(4):237-42.

[17] Yambe T, Kovalev YA, Milyagina IA, Milyagin VA, Shiraishi Y, Yoshizawa M, Saijo Y, Yamaguchi T, Shibata M, Nitta S. A Japanese-Russian collaborative study on aging and atherosclerosis. Biomed Pharmacother. 2004 Oct;58 Suppl 1:S91-4.

[18] Yamashina A, Tomiyama H, Arai T, Koji Y, Yambe M, Motobe H, Glunizia Z, Yamamoto Y, Hori S. Nomogram of the relation of brachial-ankle pulse wave velocity with blood pressure. Hypertens Res. 2003 Oct;26(10):801-6.

[19] [19] Yambe T, Meng X, Hou X, Wang Q, Sekine K, Shiraishi Y, Watanabe M, Yamaguchi T, Shibata M, Kuwayama T, Maruyama M, Konno S, Nitta S. Cardio-ankle vascular index (CAVI) for the monitoring of the atherosclerosis after heart transplantation. Biomed Pharmacother. 2005 Oct;59 Suppl 1:S177-9.

[20] Yambe T, Yoshizawa M, Saijo Y, Yamaguchi T, Shibata M, Konno S, Nitta S, Kuwayama T. Brachio-ankle pulse wave velocity and cardio-ankle vascular index (CAVI). Biomed Pharmacother. 2004 Oct;58 Suppl 1:S95-8.