Artificial Organs with Nano-technology and Development of the New Diagnosis Tool

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1. Introduction

The Aim of the research in the Medical Engineering field is the development of the new diagnosis tool and therapeutic tools for the medical fields. One example of the research theme is an artificial internal organs based on Nano-technology. As for an implantable type artificial organ, a space for implantation is restricted. Therefore, micro device development is indispensable. Nanotechnology and micromachining technology development are very important. In Tohoku University, various artificial organ development is furthered according to the tradition of Nano machine micro machine development. Various artificial organ project in Tohoku University are introduced.

2. Artificial Internal Organs for Digestive Tracts

2.1. Totally implantable artificial sphincter

After the surgery of Colon Cancer, several patients must have Stoma. And they cannot control the defecation by themselves. So, it is not so good for their quality of Lofe(QOL). The artificial sphincter that we invented makes it possible for a patient to control defecation. Therefore, we used the shape memory alloy. Two boards of a shape memory alloy were combined. Energy was transmitted by the transcutaneous energy transmission system (TETS). Figure 1 is a photograph of the animal model of the stoma. When a patient goes to a toilet, a patient brings TETS. An artificial sphincter opens and enables a patient to defecate. A patient can control defecation if this system is used. Thus, a patient's QOL will be improved greatly [1].

Fig. 1. Chrnic animal experiment of an artificial sphincter

2.2. Artificial esophagus

An about 10,000 Japanese per year died with an esophagus cancer. Everybody know that an operation of an esophagus cancer is difficult, because the reconstruction of an esophagus is needed. An operation will become easy if there is an artificial esophagus. An esophagus moves food by peristalsis. An simple pipe is not enough as an esophagus. We invented the esophagus in which a peristalsis is possible. The developed artificial esophagus consists of a macromolecule material and artificial peristalsis muscles. The Gore Tex artificial vascular graft was used as a material which suits a living body. Man's esophagus can swallow a thing by peristalsis. In order to realize a peristalsis, the shape memory alloy ring was used. The coil was made from the fiber of the shape memory alloy which improved durability by nanotechnology molecular crystal arrangement. The ring of a coil contracted in order and the peristalsis took shape. The animal experiment using the goat of the same weight as Japanese people was tried. The developed artificial esophagus was replaced with the excised esophagus. It was confirmed that the peristalsis had been realized in the body of a goat. By the artificial esophagus, an operation of an esophagus cancer becomes easy. In the future, we can undergo an operation using an endoscope with artificial esophagus. Since there is little invasion, an operation of an old man will become possible. It is expected that invention of the artificial esophagus with peristalsis movement brings big progress to esophagus cancer surgical therapy [2-7].

Fig. 2. Photograph of an artificial esophagus system

2.3. Peristalsis stent with hyperthermia function

An operation of an esophagus cancer is one of the most difficult operations even now, when medicine progressed. One of the most important points is the difficulties of esophagus reconstruction. In an operation, since the stomach and intestines are used as a substitute, an invasion becomes large and an operation of elderly people becomes difficult. Although the improvement in a life prognosis is expectable if cancer is resectable, there are a lot of cases, who were too late for surgery of the esophageal cancer at the time of diagnosis. Then, a Peristalsis Stent with Hyperthermia function for the terminal esophageal cancer patients, for whom an operation cannot be conducted, was invented. The Peristalsis Stent with Hyperthermia function has three characteristics. 1. Completely noninvasive, 2. Hyperthermia on the carcinoma tissue. 3. Peristalsis function. Possibilities are expected as one of the alternative candidates for a terminal esophagus cancer [2-7] therapy.

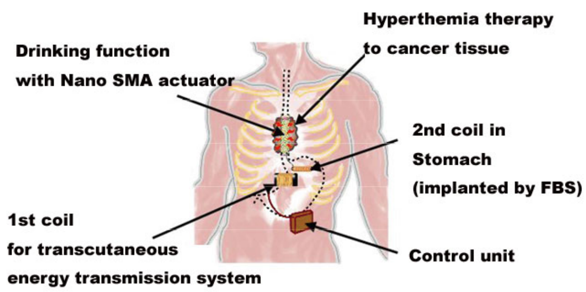

Fig. 3. Super stent system

3. Undulatrion Pump VAD Project

Rotary blood pumps (RP) are effective as small ventricular assist devices. They may be still more effective if pulsation is possible. We have studied an undulation pump (UP), which is a small RP, which can produce pulsation. In Japan, a development project of an implantable-type UP ventricular assist device (UPVAD) and UP total artificial heart (UPTAH) are underway. Six universities and some companies are together in charge of this five-year development project.

Tohoku University is investigating the influence that the UP under development has on internal-organ circulation. Goats with the same weight as Orientals were used for the experiment. The UP was implanted using the left-heart bypass system. As a result of the animal experiments, the blood circulation dynamic state was stabilized, and a sufficient left-heart-supporting effect was observed. We observed a tendency in which myocardial blood flow, and kidney blood flow changed due to UP various mode support. The problem of multiple organ failure is important during the clinical application of a ventricular assist device. Assistance for internal-organ circulation is important in preventing multiple organ failure. It is concluded that UP may be useful in preventing multiple organ failure. It was concluded that UP might be useful to prevention of multiple organ failure.

Fig. 4. Undulation Pump

4. Long Term Animal Experiments of the Evaheart

Rotary blood pumps is the most desirable VAD system when we consider the clinical application for the small people including children. Eva Heart is the rotary blood pump developed in Sun medical Co. and Chronic animal experiments for testing endurance and anti-thrombogenicity was performed in Tohoku University.

Record breaking longest survival was obtained. 823 days survival is the World Record for the totally implantable ventricular assist device in a chronic animal experiment.

Fig. 5. World record longest survival

5. Artificial Myocardium using Nano Technology.

The purpose of this research is developing nano artificial myocardium. Therefore, nano sensor development is performed. And nano control chip development is performed. An artificial myocardium actuator is also developed by nanotechnology. A control-objectives value setup which imitated baroreflex system is tried using a nano sensor and a micro control chip. As a nano sensor, by this research, the nano thin film sensor adapting diamond-like carbon (DLC) was developed, and it applied for the patent (application for patent 2003-317956).

The outstanding organism affinity can be expected and the application to the artificial organ of all fields can be expected. Furthermore, the nano sensor adapting an optical fiber was also developed and it succeeded in the animal experiment. Since information, such as each ventricle, can be evaluated simultaneously, the optimal drive of artificial myocardium is possible.

Sunagawa et al. had reported the new bionic medical treatment method which can raise a heart failure patient's probability of survival by applying a biological information and performing circulation dynamic state control. The heart failure medical treatment by carrying out pacing of both the ventricles is the established methodology. A hypothesis is drawn from these two reasons. A hemodynamics is checked by the nano sensor and it is expected that a patient's life prognosis is sharply improvable by controlling an artificial myocardium optimally. The actuator in which micro-machining is also possible is used for the artificial myocardium which this research develops.

An artificial myocardium is a system with which the pulsation of the heart is assisted. The external surface of the heart is equipped with an artificial myocardium. Therefore, like the conventional artificial heart, there is no risk of a thrombus and it does not have the problem of the durability of an artificial valve. When there is no necessity, an artificial myocardium does not operate, and since circulation is performed only with the heart, improvement in the durability of an artificial-myocardium system is expected.

Currently, artificial-myocardium research is under promotion using an electro-hydraulic system. N chronic animal experiments.

Furthermore, the molecular crystal arrangement of a shape memory alloy is prepared by application of nanotechnology. Development of the artificial muscles which have improved durability and the speed of response is progressing by reducing a hysteresis. Now, cultivation of a heart muscle cell attracts attention with reproduction medical treatment. Although it is easy to create a cell sheet, 3-dimensional construction is very difficult. Of course, reconstruction of the coronary arteries is needed, and it is apprehensive also about thrombus formation.

On the other hand, the nano level actuator by nanotechnology is important. If it succeeds in this development, it is expected that it becomes applicable to various artificial organs.

Transcutaneous energy transmission system using nanotechnology enables us the embodiment of the smaller totally implantable device.

Animal experiments were performed and the supporting effect was obtained by the mechanical assistance.

Artificial myocardium may become one of the candidates for mechanical assistance in future.

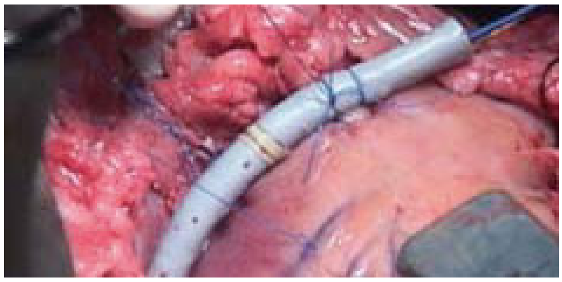

Fig. 5. Artificial Myocardium

5. Anatomical Modeling for the Cardiomyoplasty

Cardiac transplantation remains the gold standard of surgical therapies for advanced and end-stage heart failure. However, this very limited option trades one disease for another and can benefit only a small minority of patients. Heart failure is currently considered secondary to a structural increase in ventricular chamber volume or remodeling. Surgical therapies formerly contraindicated for the failing heart, as well as new therapies, can successfully affect ventricular remodeling and improve cardiac function. Surgical revascularization for patients with ejection fractions $<20\%$ is becoming common. Mitral valve repair is being explored, with surprisingly low operative mortality and encouraging intermediate results. Direct surgical approaches to restoring normal geometry and size to failing hearts, such as left ventricular reduction (Batista procedure), endoventricular patch plasty (Dor procedure), cardiomyoplasty, and prosthetic external constraints are under clinical investigation.

However, surgical procedure for the LV plasty was based on the only an experiences. No scientific knowledge was used in the surgery. So, we had invented the anatomical model for the cardiomyoplasty by the use of the information of the MRI imaging.

Fig. 6. Anatomical model for cardiomyoplasty by the use of the information of the MRI imaging

6. Brain Function Control Units

0.5-1% of the general population have the epilepsy (NIH Consensus Panel, 1990). Seizures cannot be controlled by medications in 20% of epilepsy patients. A third of these patients need the surgical resection of epileptic focus for the control of the attacks. However, surgical resection of a part of brain have a risk of complications. There is a patient who feels a sign before the convulsions of epilepsy. When feeling a sign, there is a treatment, which performs a vagal nerve stimulus. However, a stimulus of a vagal nerve is not a trustworthy treatment.

We had invented the method of cerebral partial cooling and applied for the patent (2004-304964).

By this method, if a patient feels the sign of the attack of epilepsy, a switch will be pushed. Control switch was implanted under the skin. By switch on, the focus of epilepsy is cooled and a convulsion attack is prevented beforehand. A battery is used in a patient with few attacks. Transcutaneous energy transmission system (TETS) is used in a patient with a frequent attack. In this system, if a patient feels a sign, TETS will be used. Outer coil will be attached to the inner coil under the skin. Energy is supplied and a focus is cooled. Now, we are studying the prediction algorithm of epilepsy. If prediction is possible, the automatic control of epilepsy will become possible. It is expected that it becomes good news for the patient of epilepsy [8-11].

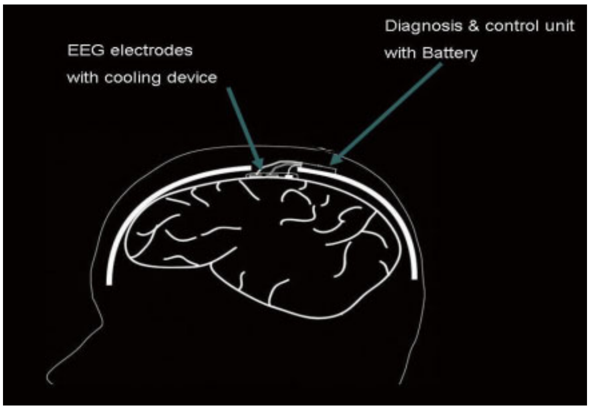

Fig. 7. Epilepsy attack control machine

7. Diagnose the Baroreflex Sensitivity of an Artery?

A baroreflex function is the one of the most important factor in the patients with hypertension. Heart rate falls reflectively at the time of a blood-pressure rise. And, an artery is extended reflectively, when blood pressure goes up. Blood pressure returns to a normal value because of heartbeat reduction and blood vessel extension.

The sensitivity of the baroreflex system is calculated at the heartbeat reaction to blood-pressure change. However, even if the reaction of a heartbeat is measured, the baroreflex function of an artery is not known. Then, we invented the new method of diagnosing the baroreflex sensitivity of an artery, using the pulse wave velocity (PWV).

Since PWV correlates with the elasticity of an artery, PWV has been used for atherosclerosis diagnosis until now. Therefore, if PWV is used, change of the elasticity of an artery can be diagnosed. The reaction of an artery can be measured if the elasticity of an artery can be diagnosed. Therefore, if PWV is measured, the baroreflex function of an artery can be diagnosed. However, even if it refers to medline and searches a patent, there is no report of a method which measures a baroreflex sensitivity by PWV, until now.

Therefore, this report is the first in the world. By ten healthy objects, the time series of a heart rate variability, fingertip pulse change, and blood pressure was recorded. The obtained data were inputted into PC through the AD converter.

Preventive medicine is a priority for most governments because of increasing medical and health care expenses [12,13]. In Japan, the concept of metabolic syndrome has recently been identified to play an important role in the pathophysiology of many diseases [14-17]. Hypertension, hyper-lipidemia, diabetes mellitus, and obesity are important consequences of metabolic syndromes. Among these, hypertension is paramount when considering disruption of organ function [18,19]. Thus, prevention of hypertension is very important.

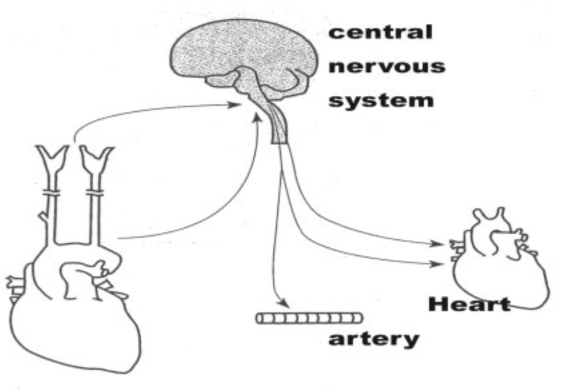

Fig. 8. Schematic diagram of the baroreflex system

The baroreflex system is a key indicator of hypertensive pathophysiology [20,21]. When blood pressure (BP) increases, heart rate (HR) decreases, and there is peripheral arterial dilation [22,23]. 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 [24,25]. Baroreflex sensitivity is reduced in younger hypertensive patients [24-26].

However, currently there is no simple and sensitive diagnostic method to measure the arterial behaviour in the baroreflex system.

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

7.1 Diagnosis of arterial baroreflex sensitivity

Every medical student studies the baroreflex system as a typical example of homeostasis [22-26]. When blood pressure increases, baroreceptors in the carotid arteries and aortic arch sense the increase in the baroreflex sensitivity. When this information was transmitted to the central nervous system, the HR lowers and arteries dilate. These reactions restore the normal BP (Fig. 8).

Baroreflex sensitivity was evaluated by measuring the HR response to the BP changes (Fig. 9).

The slope of the linear regression line demonstrated the sensitivity of the baroreflex system of the heart.

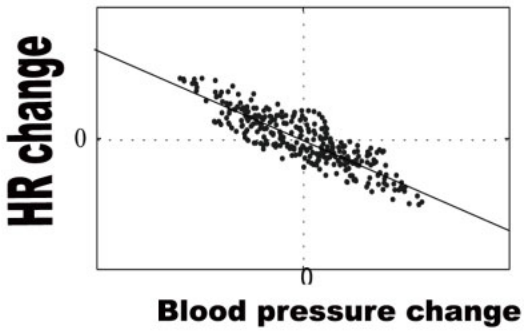

Fig. 9. Baroreflex sensitivity of the heart.

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 — brachial ankle pulse wave velocity (baPWV) and cardio-ankle vascular index (CAVI) - have been developed to evaluate human arterial stiffness [27-30].

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 (Fig. 10). BP will return to normal because of the decrease in resistance. The softness of an arterial wall can be measured by PWV.

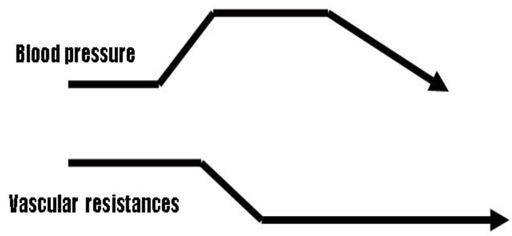

Fig. 10. Schematic representation of the time series response data for the vascular resistance of the baroreflex system.

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. 11).

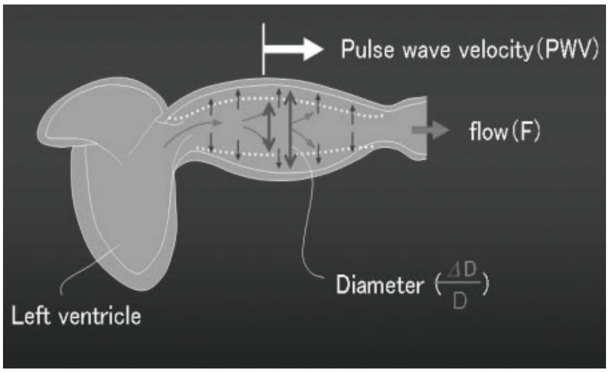

Fig. 11. Schematic illustration of PWV.

Thus, measurements of PTT and BP permit an evaluation of arterial baroreflex response.

7.2. Animal experiments

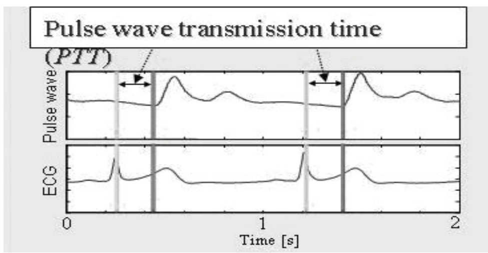

Fig. 12. Time series data of ECG, PWV and PTT.

To evaluate the autonomic responses of the PTT or PWV, chronic animal experiments were carried out using healthy adult goats. The goats used in the experiment had weighed almost the same as an average Japanese person. All experiments were approved by the Ethical

Committee of the Institute of Development, Aging and Cancer, Tohoku University. Under anaesthesia, the chest cavity was opened in the fourth intercostal space. Implants included an electromagnetic flow meter, electrodes for electrocardiogram (ECG), catheter-tip pressure sensor inserted into the femoral artery and 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.

After intravenous injection with methoxamine, BP suddenly increased (Fig. 13).

HR reduced in response to the increase in systolic pressure, and PTT increased in response to the BP change. Prolongation of the PTT indicated the softening of the artery. Therefore, PTT and PWV were thought to be indicative of the autonomic response of an artery.

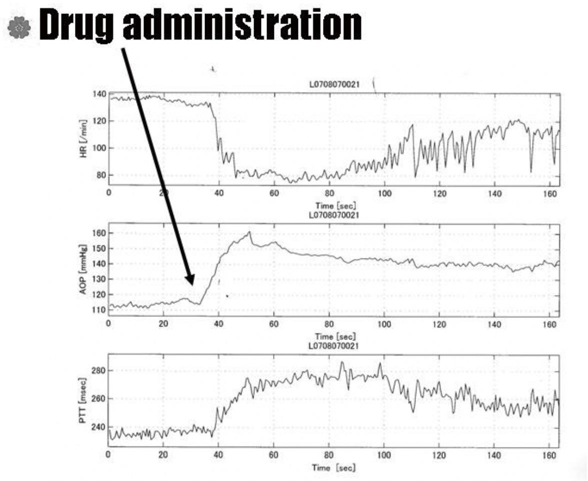

Fig. 13. Time series data of the HR, systolic BP and PTT in a healthy and conscious adult goat.

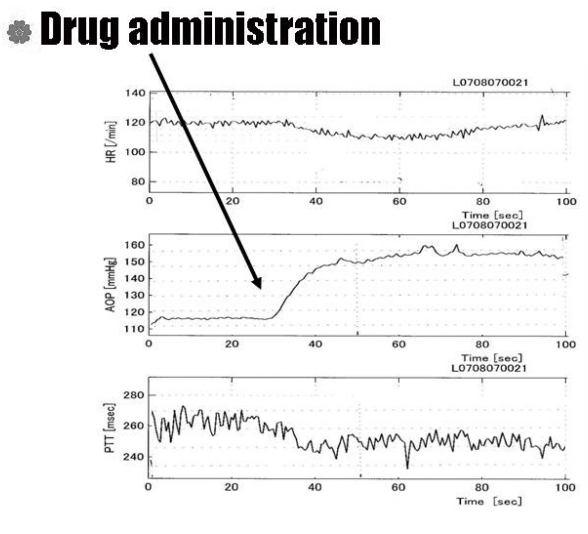

Fig. 14. Time series data of the HR, systolic BP, and PTT in a healthy and conscious adult goat after complete blockage of an autonomic nervous system using atropine and propranolol.

To demonstrate the autonomic nervous control of the HR and PTT, the autonomic nerves were blocked using atropine and propranolol [31,32]. During this blockage, the HR did not respond to the BP change; however, the 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.

7.3. Measurement equipment and analysis

PTT and PWV were easily measured by monitoring ECG and pulse wave. Figure 15 shows the equipments used for the measurement. The newly developed system used only an ECG and a pulse wave recorded from the radial artery or fingertip. These time series were inputted into a personal computer, and analyzed quantitatively using a custom-developed software.

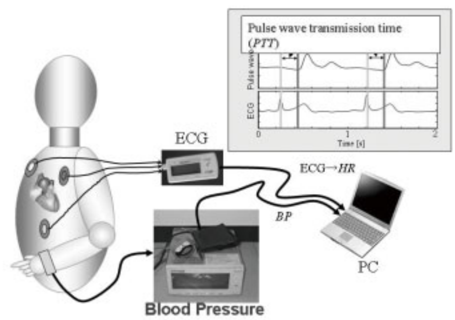

Fig. 15. A schematic illustration of the measurement equipment.

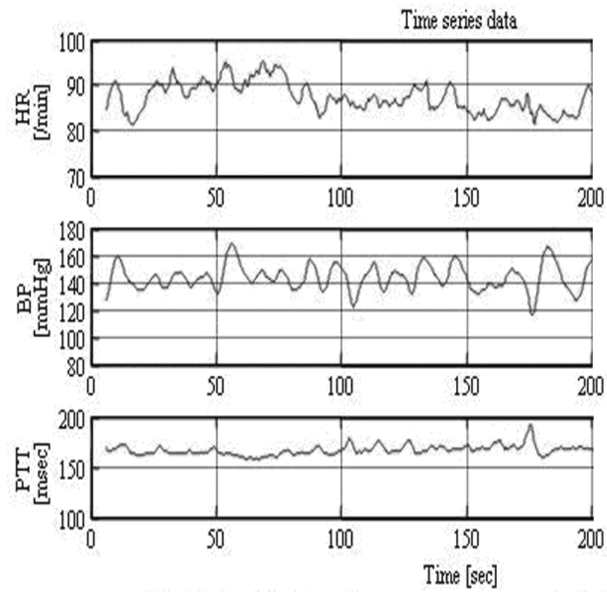

Fig. 16. Time series data of the HR, BP and PTT.

The time series for HR, BP, and PTT are depicted in Fig. 16 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 spline functions to continuous-time functions, and were resampled every 0.5 s.

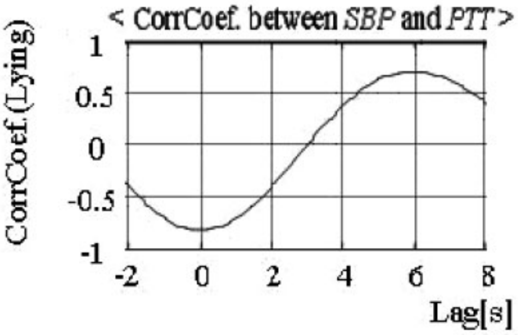

Fig. 17. An example of the cross-correlation function between the systolic BP and PTT.

Figure 17 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, 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.

Figure 18 displays an example of the correlation between the systolic BP and PTT. PTT was plotted after 6.0 s. 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.

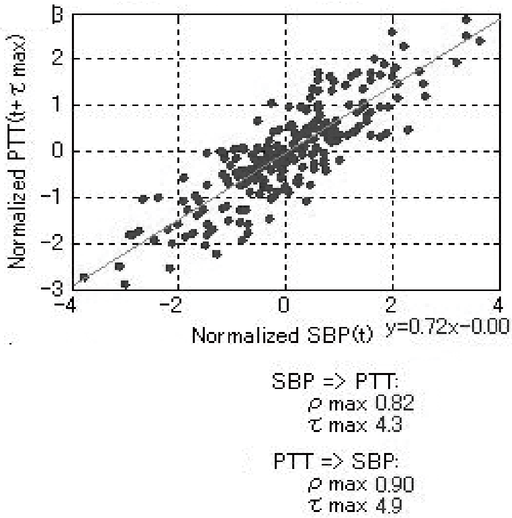

Fig. 18. An example of the correlation between the normalised systolic BP and normalised PTT in a patient.

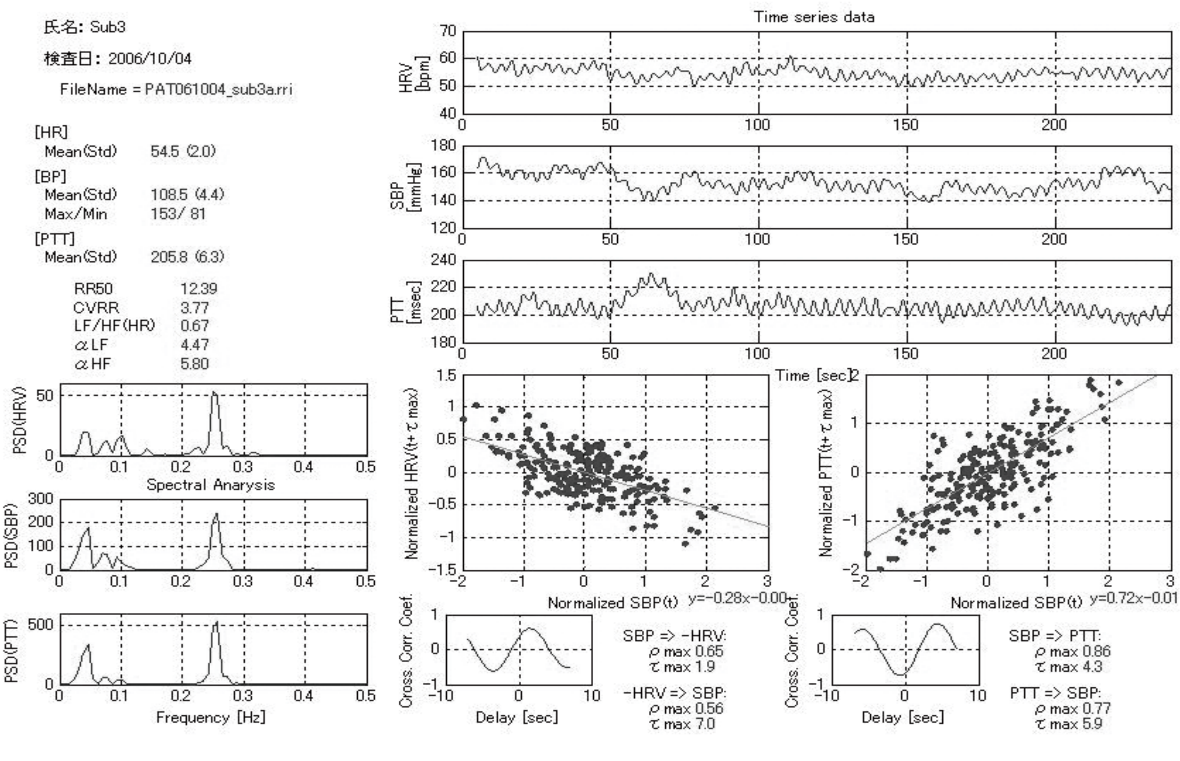

Fig. 19. Patient report to evaluate the baroreflex sensitivity of heart and artery

7.4. 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. Slope of the changes in BP and HR indicates the sensitivity of the baroreflex system of heart. Furthermore, this system could also measure the sensitivity of the baroreflex system of an artery.

Figure 20 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 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 ethical committee allowance. So far, the results have shown that our system can successfully detect decreased sensitivity of the baroreflex system in hypertensive patients. We are now analyzing the various data of the patients with hypertension.

Further examination will be needed using more cases. This new method may be useful to follow up patients with hypertension.

8. Baroreflex in Total Artificial Heart

Several investigators suggested that hypertension was observed after total artificial heart (TAH) implantation in chronic animal experiments. One of the most important indicators of the pathophysiology in hypertension is the baroreflex system. When blood pressure increases, heart rate decreases and there is peripheral arterial dilation. By decreasing the cardiac output and peripheral arterial resistances, blood pressure returns to normal. However, there is no response in HR in TAH animals, and we cannot observe the HR response after TAH implantation, because there is no heart.

Presently, we report the development of a method and associated hardware that enables the diagnosis of baroreflex sensitivity by measuring the responses of the artery. The measurements are obtained by monitoring an electrocardiogram and a pulse wave recorded from the radial artery or fingertip in this system. The time series of measurements is inputted into a personal computer for quantitative analysis using a custom-developed software. 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. In this system, the changes in the PTT in response to the blood pressure changes were observed.

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 was easily obtained and it demonstrated the sensitivity of the baroreflex system of an artery. This system can be used even if there is no heart. This system may be useful when we consider the ideal treatment and follow up of the patients after TAH implantation.

Fig. 20. Total artificial heart

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