

recordings based on multivariate parametric identification," *IEEE Trans Biomed Eng*, vol. 44, No. 11, pp. 1092-101, 1997.

- [5] N. Sugita, M. Yoshizawa, A. Tanaka, K. Abe, S. Chiba, T. Yambe, S. Nitta, "Quantitative evaluation of the effect of visually-induced motion sickness using causal coherence function between blood pressure and heart rate", Proc. of 26th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2004
- [6] A. Porta, R. Furlan, O. Rimoldi, M. Pagani, A. Malliani, P. van de Borne, "Quantifying the strength of the linear causal coupling in closed loop interacting cardiovascular variability signals.", *Biological Cybernetics* vol. 86, pp. 241-251, 2002

Simulation of Atrial Wall Suction in a Continuous Flow Total Artificial Heart Model

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Abstract: An existing mathematical model of the cardiovascular system was modified by replacing the ventricles of the natural heart with two rotary blood pumps to investigate the problem of atrial wall suction in a continuous flow total artificial heart system and provide preliminary data for the implementation of an anti-suction control algorithm with quicker response. The responses of left atrial pressure to changes in right pump output were investigated through computer simulations using the modified model. The results were then compared with actual data from a prior acute animal experiment with a healthy mature goat performed to obtain data on pulmonary circulation dynamics and to determine the conditions that lead to atrial wall suction. The simulation results showed significant agreement with the animal experiment data with regards to left atrial pressure response to changes in right pump speed. Atrial wall suction was also successfully simulated using this model.

Keywords: artificial heart, simulation, cardiovascular model.

1. INTRODUCTION

Non-pulsatile or continuous flow mechanical circulatory devices such as centrifugal (rotary) blood pumps and axial-flow blood pumps have been considered as practical alternatives to currently available pulsatile devices for artificial heart applications [1, 2]. This is largely due to their small size and lower manufacturing costs compared to current pulsatile devices. For Japanese patients who require circulatory assistance in the form of an implantable ventricular assist device (VAD) or a total artificial heart (TAH), size is a vital factor due to the smaller volume of the thoracic cavity of the average patient. Implantable systems currently available in other countries are, in most cases, too large for the average Japanese patient. This has given rise to a number of research studies in Japan aiming for the development of smaller devices. In addition, recent studies indicating no difference between pulsatile and continuous flow devices with regards to the neurocognitive function in patients with VADs contribute positively to the ongoing discussion on the advantages and disadvantages of non-pulsatile perfusion [3].

However, unlike pulsatile devices wherein cardiac filling and cardiac ejection are performed asynchronously, continuous flow devices draw in blood from the atrium or ventricle and eject the same amount of blood through the outflow cannula simultaneously. This makes it more prone to atrial or ventricular wall suction compared to pulsatile devices. Even in an undulation pump operating in pulsatile mode, atrial suction could cause problems that could result in the termination of the subject [4].

The primary cause of atrial wall suction is insufficient blood volume in the atrium. Consider the left atrium in a continuous flow TAH. A sudden

increase in left pump rotational speed would draw out a large amount of blood from the atrium in a short time. Venous return would not be able to compensate for this deficiency unless purposely increased. Thus, blood volume in the atrium would continue to decrease until the negative pressure inside the atrium causes the atrial wall to be sucked into the inflow cannula [5].

Secondary causes of atrial wall suction are the shape of the cannula tip used and the positioning of the cannula inside the atrium. Proximity of the cannula tip to the atrial wall increases the risk of atrial wall suction.

The most common and direct way to recover from atrial wall suction is to decrease the rotational speed of the pump. However, this is not desirable when performing automatic physiological control because it would disrupt normal perfusion to the systemic circulation. Another method is to perform left-right balance control wherein the left and right atrial pressures are maintained at the same level. This method can function improperly when the left atrial pressure drops to a low level because the balance control algorithm will tend to keep it at that low level, which is not desirable for extended periods of time. Another issue when using the left-right balance control is the time delay present between the right pump and the left atrium.

Changes in the output of the right pump in a continuous flow artificial heart system directly affects left atrial pressure (*LAP*). However, the effect on *LAP* by the changes in right pump output is not instantaneous but is time delayed due to the presence of hydraulic resistances and compliances in the pulmonary circulation [6].

In a previous study, we verified the possibility of preventing left atrial wall suction in a continuous flow total artificial heart (CFTAH) by controlling the output

of the right pump instead of the left pump [5]. By increasing right pump output when left atrial pressure (LAP) falls below a certain threshold level, we were able to prevent further progress of atrial wall suction in its early stages. However, practical application of this method requires a quicker response time and guaranteed prevention of sudden increases in pulmonary arterial pressure. To solve these problems, pulmonary circulation dynamics have to be considered thoroughly. If the dynamic characteristics of the pulmonary circulation could be approximated as a linear system, it would be possible to introduce an adaptive control algorithm to compensate for individual differences and temporal changes due to the system dynamics [7].

In this study, we investigated pulmonary circulation dynamics by observing the effect of changes in right pump output on LAP when a continuous flow blood pump is connected as a TAH in a healthy, mature goat. We also observed certain conditions that contributed to the occurrence of atrial wall suction. Based on these results, we developed a model based on an existing mathematical model of the cardiovascular system. We performed simulations in an attempt to reproduce the conditions observed in the animal experiment and compared the results to the animal experiment data.

2. METHODS

2.1 Simulation Model

The mathematical model employed in the study is based on an existing model by Ursino [8]. The modifications applied to this model include the replacement of the ventricular model with a rotary pump model and the introduction of a non-linear resistance between the atrium and the cannula connecting it to the pump. An electrical circuit representation of the modified model is shown in Fig. 1.

The rotary pump model used is based on previous studies by Nishida, *et al.* on the development of automatic flow control methods for the Terumo Capiox SP-101 centrifugal pump [9].

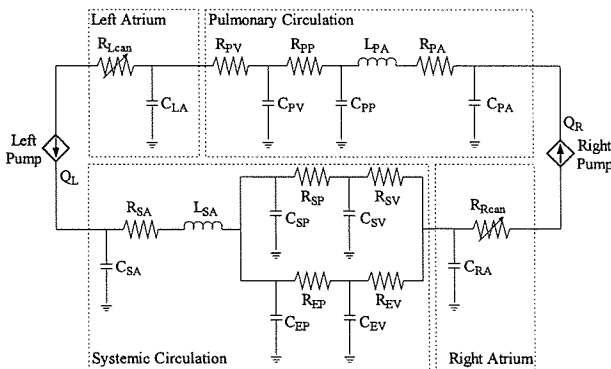


Fig. 1. Circuit representation of the cardiovascular system model modified for the CFTAH system.

R, hydraulic resistances; C, compliances; L, inertances; Q, flow rates.

The relationship between the flow rate, pump rotational speed, and pump pressure is shown as,

$$Q = \frac{\left(92.6 \left(\frac{N}{1000}\right)^2 - P\right)}{3.5} \quad (1)$$

where Q is the pump flow rate (L/min), N is the pump rotational speed (rpm), and P is the differential pressure (mmHg) between the pump inlet and outlet.

To simulate atrial wall suction, a non-linear resistance was introduced in the atrio-cannular coupling. The slope of the resistance in the cannula inlet increases acutely as the decreasing atrial volume approaches a certain value V_0 . A further simplification of this non-linear resistance is shown in Fig. 2. The cannula inlet resistance R_{Lcan} has a constant value R_0 when atrial volume V_{LA} is greater than V_0 and an infinite value when less than V_0 . This effectively reduces pump flow rate to zero when atrial blood volume decreases below the threshold level V_0 , which is similar in effect to the blocking of the cannula inlet by the atrial wall.

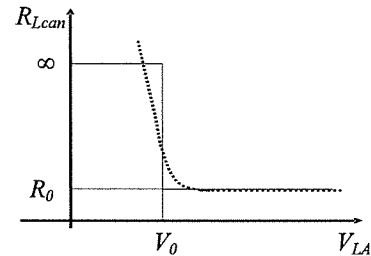


Fig. 2 Non-linear atrio-cannular resistance introduced to facilitate the simulation of atrial wall suction.

Right pump flow rate is computed using Eq. (1). Applying the conservation of mass and balancing the forces in the pulmonary arteries gives

$$\frac{dP_{PA}}{dt} = \frac{1}{C_{PA}} (Q_R - Q_{PA}) \quad (2)$$

$$\frac{dQ_{PA}}{dt} = \frac{1}{L_{PA}} (P_{PA} - P_{PP} - R_{PA} Q_{PA}) \quad (3)$$

From the pulmonary peripheral circulation, we get

$$\frac{dP_{PP}}{dt} = \frac{1}{C_{PP}} \left(Q_{PA} - \frac{P_{PP} - P_{PV}}{R_{PP}} \right) \quad (4)$$

While the conservation of mass at the pulmonary veins gives,

$$\frac{dP_{PV}}{dt} = \frac{1}{C_{PV}} \left(\frac{P_{PP} - P_{PV}}{R_{PP}} - \frac{P_{PV} - P_{LA}}{R_{PV}} \right) \quad (5)$$

$$\frac{dP_{LA}}{dt} = \frac{1}{C_{LA}} \left(\frac{P_{PV} - P_{LA}}{R_{LA}} - \frac{P_{LA} - P_{Lin}}{R_{Lcan}} \right) \quad (6)$$

Where P_{Lin} is the pump inlet pressure. LAP is denoted by P_{LA} to preserve uniformity in the equations. The first

term in brackets in Eq. (6) is venous return and the second term is the rate of blood flow pumped out of the left atrium.

The variable cannula inlet resistance R_{Lcan} is given by

$$R_{Lcan} = \begin{cases} \infty & , V_{LA} \leq V_0 \\ R_0 & , V_{LA} > V_0 \end{cases} \quad (7)$$

where left atrial volume V_{LA} is computed by

$$\frac{dV_{LA}}{dt} = C_{LA} \cdot \frac{dP_{LA}}{dt} \quad (8)$$

The model was implemented using Simulink (The Mathworks, Inc., Natick, MA). Numerical integration of differential equations was performed using the Runge-Kutta method. The parameters used in the simulation model were interpolated from values taken from literature to suit a 60-kg body weight, which was the weight of the subject in the animal experiment.

2.2 Animal Experiment

In order to verify the validity of the simulation model, a qualitative comparison was made between the results obtained from the simulation and the results obtained from a prior animal experiment.

In the animal experiment, two commercially available centrifugal blood pumps (Capiiox SP-101, Terumo Corp., Tokyo., Japan) were connected extracorporeally to the circulatory system of a healthy mature goat. The inflow cannula of the left pump was sutured to the left atrium and the outflow cannula was anastomosed end-to-side with the descending aorta. The right pump was similarly connected to the right atrium and the pulmonary artery.

Natural heart function was terminated and the continuous flow pumps were operated as a TAH system. The output of the right pump was increased or decreased in a step-like waveform while the left pump output was kept constant.

Pump flow rates were measured using ultrasonic flow meters (Transonic Systems Inc., Ithaca, NY) attached to the outflow cannulae. Aortic pressure AoP , pulmonary arterial pressure PAP , left atrial pressure LAP and right atrial pressure RAP were measured with fluid-filled catheters and pressure transducers. All measurements were monitored in real-time on a computer running LabVIEW (National Instruments Corp., Austin, TX) and recorded on hard disk and on DAT. Pump output was controlled from the LabVIEW program through a serial interface connected to the pump drivers.

3. RESULTS

The time constant present in LAP response to right pump speed was calculated from the shape of the graphs shown in Fig. 3. The resistance and compliance parameters in the pulmonary circulation of the model were tweaked to reflect this time constant. LAP response to a step-like increase and step-like decrease in right pump rotational speed can be seen as a gradual increase characteristic of a RC filter step response.

Fig. 4 shows the simulation of atrial wall suction. The non-linear atrio-cannular resistance introduced in the modified model has a constant value until the atrial volume V_{LA} decreases to an arbitrarily assigned value V_0 . As the atrial volume continues to decrease, the atrio-cannular resistance reverts to an infinite resistance and reduces flow rate to zero. During this period, venous return continues to fill the left atrium and increase atrial blood volume past the threshold limit of V_0 , which switches the atrio-cannular resistance back to its constant value causing pump blood flow to resume. This cycle is repeated until there is sufficient blood volume in the left atrium to meet physiological demand and maintain atrial blood volume above the threshold level.

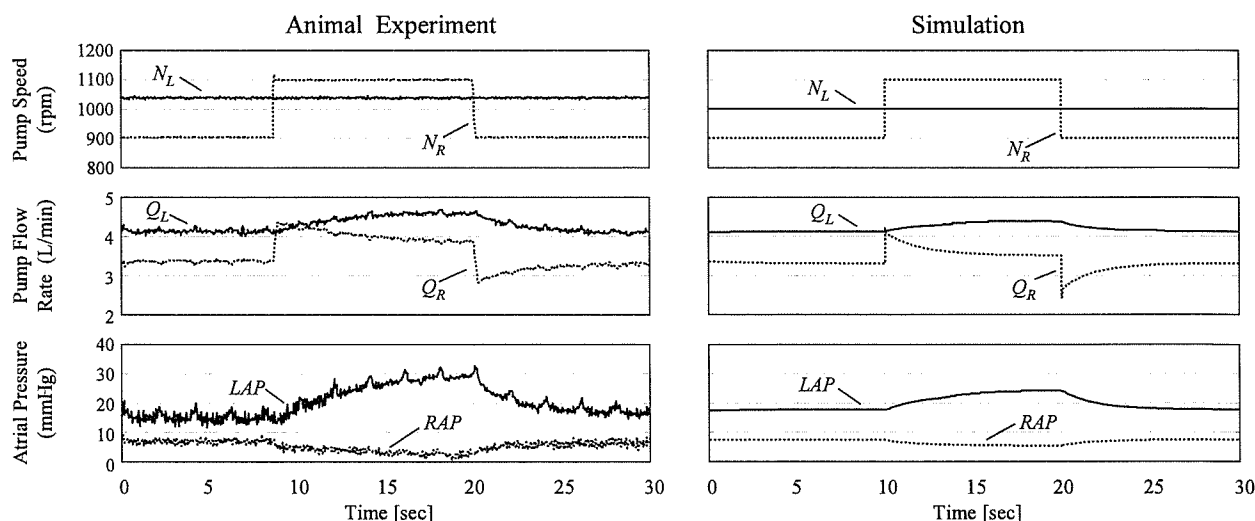


Fig. 3. LAP response to step increase and decrease in right pump rotational speed.

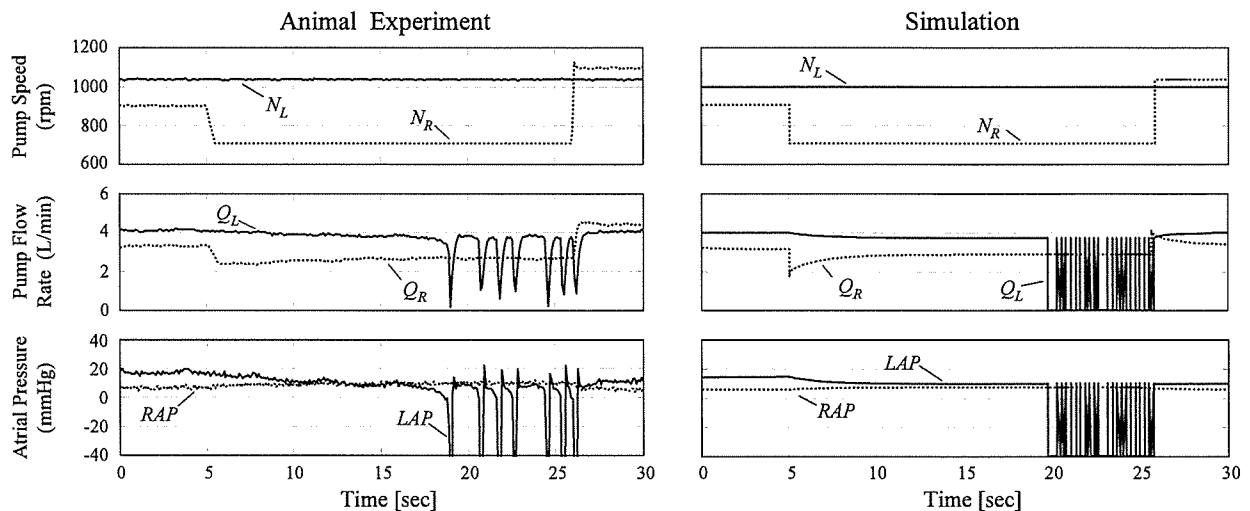


Fig. 4. Simulation of atrial wall suction by decreasing right pump output.

4. CONCLUSION

LAP response to step-like changes in right pump output was successfully simulated in the modified model. These results showed significant agreement with results obtained from a prior acute animal experiment.

Simulation of atrial wall suction was also successful. However, other conditions that may lead to atrial wall suction, such as abrupt increase of left pump output and effects of drug application, were not investigated and should therefore be included in future experiments.

Since atrial wall suction was successfully simulated, the modified simulation model may be used to evaluate anti-suction control algorithms that have a faster response time compared to existing methods without interrupting the systemic circulatory control of the left pump.

REFERENCES

- [1] Y. Nosé, K. Kawahito, and T. Nakazawa, "Can We Develop a Nonpulsatile Permanent Rotary Blood Pump? Yes, We Can," *Artificial. Organs*, Vol. 20, No. 4, pp. 467-474, 1996.
- [2] C. D. Bertram, "Measurement for implantable blood pumps," *Physiological Measurement*, Vol. 26, pp. 99-117, 2005.
- [3] D. Zimpfer, G. Wieselthaler, M. Czerny, R. Fakin, D. Haider, P. Zrunek, W. Roethy, H. Schima, E. Wolner, and M. Grimm, "Neurocognitive Function in Patients with Ventricular Assist Devices: A Comparison of Pulsatile and Continuous Blood Flow Devices," *ASAIO Journal*, Vol. 52, pp. 24-27, 2006.
- [4] Y. Abe, T. Chinzei, T. Isoyama, S. Kobayashi, T. Ono, I. Saito, K. Iwasaki, M. Ishimaru, A. Baba, A. Kouno, T. Ozeki, T. Tohyama, and K. Imachi, "Advance in Animal Experiments with the Undulation Pump Total Artificial Heart: 50 and 54 Day Survival Periods with 1/R Control," *ASAIO Journal*, Vol. 49, pp. 325-332, 2003.
- [5] P. Olegario, M. Yoshizawa, A. Tanaka, K. Abe, H. Takeda, T. Yambe, and S. Nitta, "Outflow control for avoiding atrial suction in a continuous flow total artificial heart," *Artificial Organs*, Vol. 27, pp. 92-98, 2003.
- [6] A. M. Katz, *Physiology of the Heart*, Lippincott Williams & Wilkins, Philadelphia, PA, 2001.
- [7] A. Tanaka, M. Yoshizawa, K. Abe, T. Yambe, S. Nitta, "Application of adaptive pole assignment method to vascular resistance-based control for total artificial heart," In: H. Koyanagi, T. Akutsu, eds. *Heart replacement-artificial heart 6*, Springer-Verlag, Tokyo, Japan, 1998.
- [8] M. Ursino, "Interaction between carotid baroregulation and the pulsating heart: a mathematical model," *American Journal of Physiology, Heart and Circulatory Physiology*, Vol. 275, pp. H1733-H1747, 1998.
- [9] H. Nishida, T. Nishinaka, M. Endo, H. Koyanagi, H. Oshiyama, A. Nogawa, and T. Akutsu, "Clinical Application of a Newly Developed Autoflow Control System for the Terumo Centrifugal Pump: From External Control to Built-In Direct Control," *Artificial Organs*, Vol. 20, pp. 625-631, 1996.

Development of Implantable Probe for Observation of Microcirculation

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It is a long-term controversial point between the circulatory physiologists and the artificial heart researchers whether the pulsatile flow is essential for the living body or not [1]. In particular, since the axial flow pump, a continuous flow pump, that could keep the patients alive for more than a few years was introduced into use in clinical setting in 2001, this problem has been regarded as a very important physiological and pathophysiological issue. The objective of this study was to develop an implantable probe to observe microcirculation in artificial circulation.

The principle of the probe developed in this study is the following: a thin living tissue is put directly on a highly integrated CCD (charge coupled device), and it is illuminated from the backside of the tissue with LED (light emitting diode). The microvascular nets in the tissue will be projected on the CCD surface, like a contact photograph, which produces an image on the TV screen. The problems are how to magnify them to be able to observe the erythrocyte flow, how to control the focus, how to electrically insulate them and how to make them compact.

After several attempts to magnify the image, a micro lens having 2 mm in diameter, 2 mm long and 6 times magnification, was designed and made of acrylic resin. The lens was installed into a CCD camera with 8 mm in diameter and it was 60 mm long. The camera could magnify the image about 650 times on the 14 inches TV screen. A distinct microcirculation image, including the capillary flow, could be observed when the camera was implanted into the connective tissue under the skin of the rabbit. Now the focus control system is being developed with the camera to be implanted in animals on the long-term base.

K e y w o r d s: microcirculation, pulsatility, continuous flow, CCD (charge coupled device), artificial heart

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1. Introduction

Pulsatility of the circulatory system had been believed to be essential in the living body before Nose et al. succeeded in keeping a calf alive for 90 days under the continuous flow condition with the centrifugal blood pump in 1978. Moreover, many kinds of continuous flow ventricular assist devices (VAD), the axial flow pump and the centrifugal pump have begun to be used clinically as a bridge to heart transplantation since 2000. Although many patients with the implanted continuous flow VAD can survive for more than a few years, their aortic flow has pulsatility by their own residual heart beat. So it is still an important controversial issue whether the pulsatility is essential or not for the living body in normal survival.

It would be very important to observe the micro-circulation to evaluate the necessity of pulsatility. However, there is no way to continuously observe the microcirculation without anesthesia in the animal model. We have been developing an implantable probe for a long-term observation of microcirculation since 1987. In this article, the authors would like to introduce the historic and the present status of the probe.

2. Materials and Methods

2.1. CCD Probe for the Contact Observation of Microcirculation [2-5]

The first idea to develop a probe was based on the following principle. As the integration of the CCD (charge coupled device) has been increasing due to the development of micro- and nano-technology, the authors thought that microcirculation could be observed without the lens like a contact photograph by direct contacting the living tissue with the CCD surface and lighting it from the back side of the tissue (Fig. 1). The micro-vasculature was projected on the TV screen by putting the rat mesentery on the CCD enveloped with a thin transparent film for electrical insulation. Then the first probe was developed in the following manner. A 0.5-inch CCD with 250 K or 400 K pixels was used in this study. As the CCD surface is 1.5 mm below the edge of the ceramic package after removal of its cover glass, a fiber optic plate (FOP), which is a 2 mm long integrated hexagonal core glass rod that could conduct an image from one end to another without distortion, was adhered onto the CCD surface to ensure a good contact between the tissue and the CCD surface. The residual gap in the ceramic package was filled up with room temperature vulcanized (RTV) silicone adhesive or epoxy resin, and the outside of the package, including the lead wires, was molded with epoxy resin to provide electrical insulation. A LED was fixed into the center of the CCD, 10 mm above the FOP with a specially designed micro-stand. Figure 2 shows a scheme of the probe. Figure 3 shows a photograph of subcutaneous connective tissue of a rabbit taken by this probe. An arteriole and venule with a diameter as small as 20–30 μm could be observed.

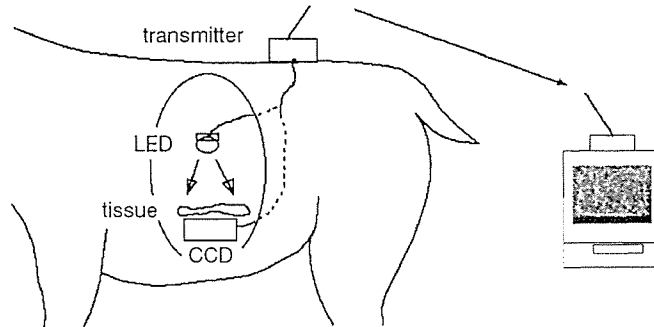


Fig. 1. The principle of the implanted probe to observe the microcirculation

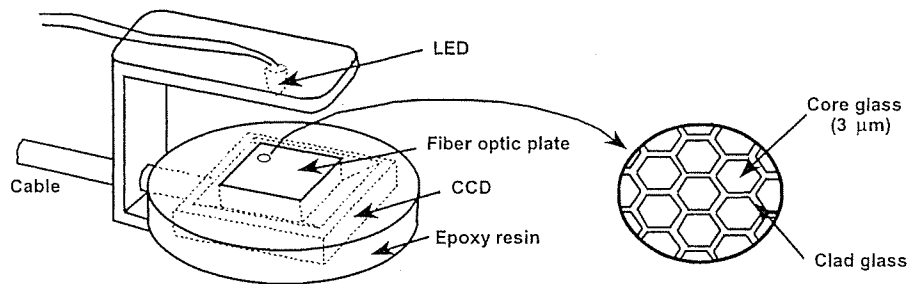


Fig. 2. Fabrication of the implantable probe using FOP

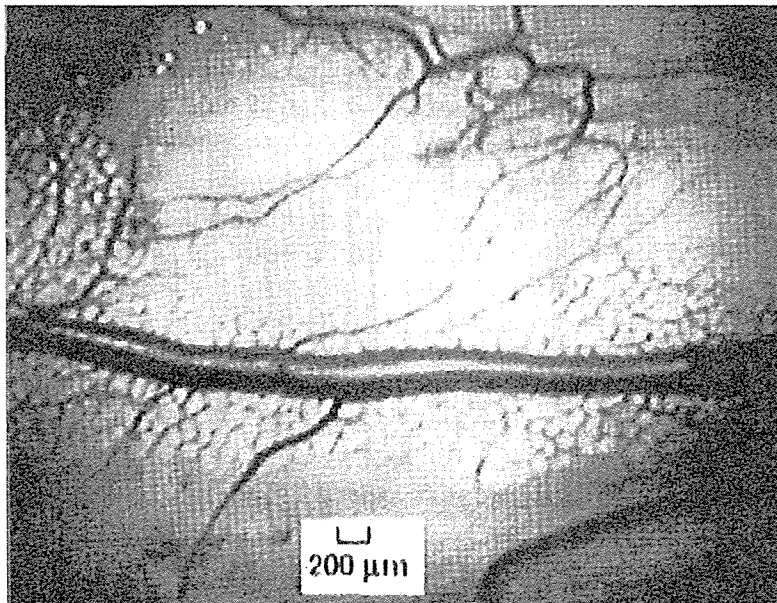


Fig. 3. Microvasculature of connective tissue in rabbit

A higher degree of magnification was required to observe the capillary circulation. A new probe used the tapered FOP, which could magnify the image 3 times, was designed as shown in Fig. 4. The tissue on the probe was magnified 165 times on the 14 inches TV screen. Figure 6 is a photograph of rat mesentery taken by this probe. The capillary vessels could be recognized with their circulation.

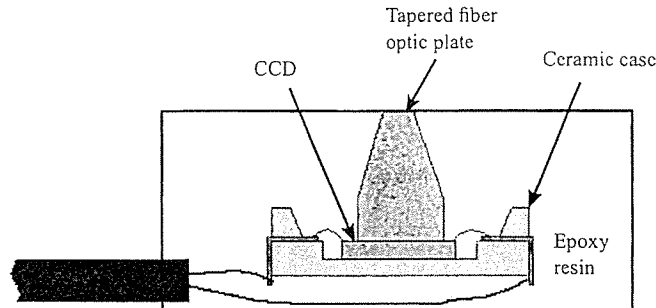


Fig. 4. Probe with a tapered FOP having 3 times magnification

2.2. Implantable Probe with a Micro-lens

One of the problems of the contact observation probe using the tapered FOP was a difficulty in getting a finely focused image in the case of the thickened tissue, such as omentum and fascia. A micro-lens system with a focus mechanism was required to be developed.

A single micro-lens with 4 mm in diameter and 4.2 mm long was made from acrylic resin. It is aspheric and has 3 times magnification. The lens was fabricated with the CCD camera as shown in Fig. 5. The distance between the objective and the lens and the lens and the CCD surface was 3 and 9 mm, respectively. The real magnification on the 14 inch TV screen was 165 times in the *in-vitro* experiment.

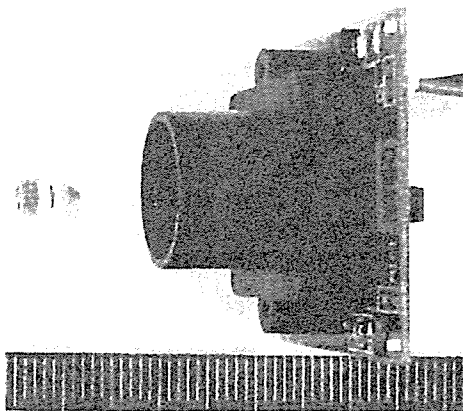


Fig. 5. The micro-lens and the CCD camera

Three types of focusing mechanisms, the screw type, the gear and cam type and the air bag type were tested. Figure 6 shows the screw type probe, in which the focus was adjusted by turning the stage. It was implanted into a goat as shown in Fig. 7. This goat was the first animal observing its own microcirculation. However, in this system, the focus could not be adjusted from outside the body after implantation. A gear train and a cam focus adjust system, in which the revolution number of the

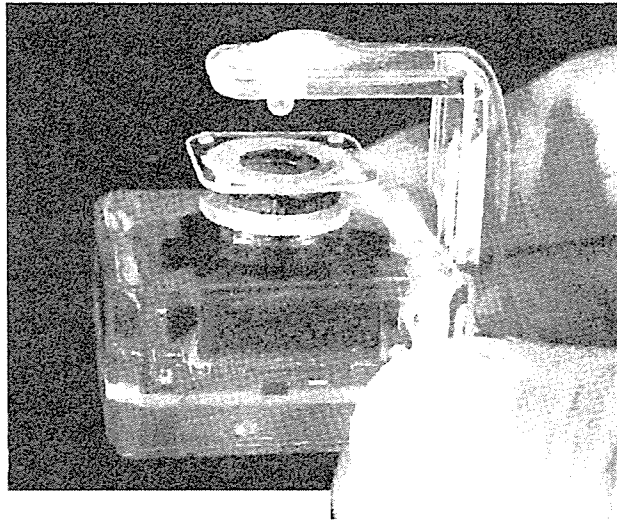


Fig. 6. The implantable probe with the screw type focus adjust system



Fig. 7. The first goat observed its own microcirculation

micro-motor was reduced by the gear train and the cam control the focus position, was difficult to precisely adjust to the focus, and the size of the probe became big. The air bag type focus adjust system, in which the focus could move precisely by inflation and deflation of the air in the bag from outside the body, was the best from the view points of its accuracy and dimensions. The CCD with a driver and micro-lens was packed into an acrylic resin case (37x37x38 mm) with a thin transparent stage to put a living tissue on it. The air bag placed at the back side of the CCD unit, could inflate and deflate from the outer side and precisely change the distance between the lens and the stage for focusing. The probe was implanted into a rabbit, and subcutaneous connective tissue and/or fascia was fixed on the stage. A weak light from LED was projected from the backside of the tissue. The CCD image was sent out to the TV by a transmitter fixed on the skin. The flow of erythrocytes and leukocytes in the capillaries as well as in the arteriole and venula could be observed on the TV screen as shown in Fig. 8.

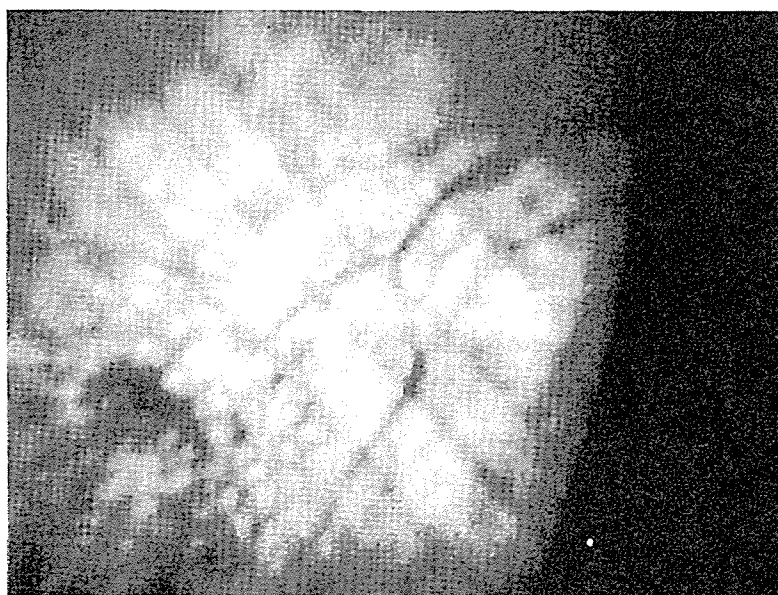


Fig. 8. Microcirculation in the fascia of the rabbit

2.3. Development of an Implantable Probe with a High Degree of Magnification

Although the capillary flow could be observed in the last model, its magnification and resolution were insufficient to analyze the erythrocyte speed, the diameter change in the arteriole. The size reduction of the probe is another important problem to be addressed in the long-term implantation in the animal model. A new probe with high magnification and of a smaller size was designed. A micro-lens having 2 mm in diameter, 2 mm long and 6 times magnification was designed, and it was made

of acrylic resin. The lens was installed into a CCD camera with 8 mm in diameter and 60 mm long (Fig. 9). The probe could magnify the image on the stage about 650 times on the 14 inch TV screen. An acute experiment was performed with a rabbit. The probe could be easily inserted. A distinct microcirculation image including the capillary flow could be observed when the camera was inserted into the subcutaneous connective tissue (Fig. 10).

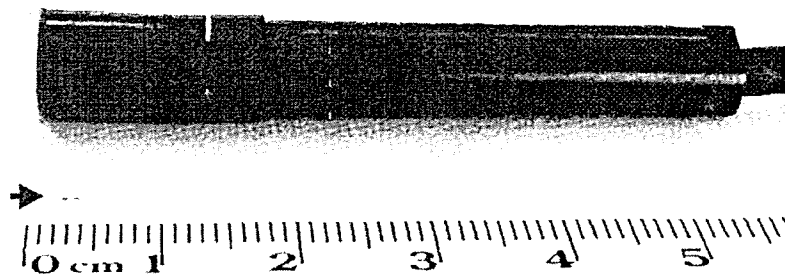


Fig. 9. The newly developed micro-lens (arrow) and the probe

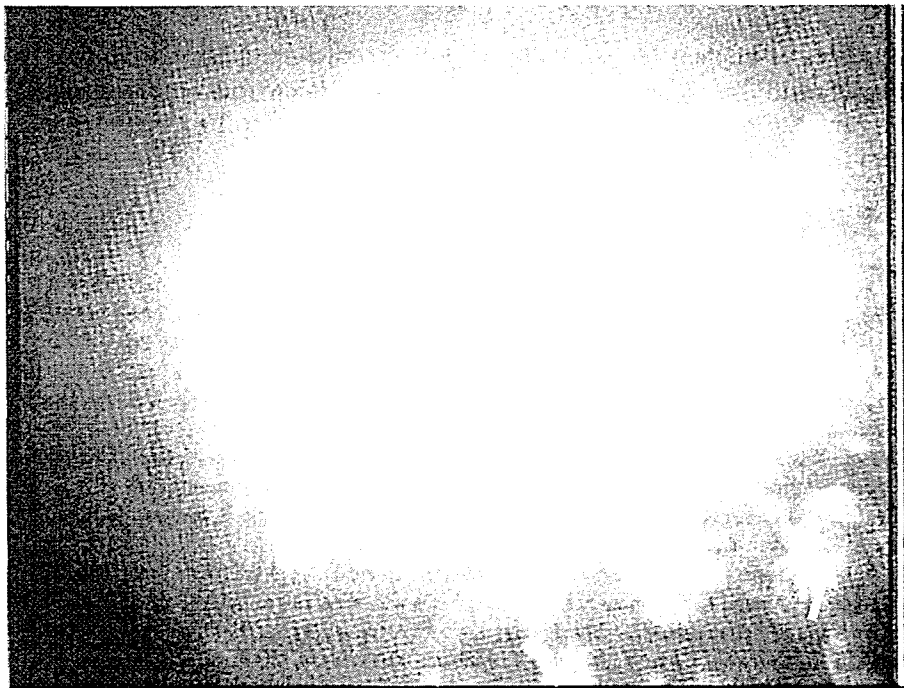


Fig. 10. Microvasculature of the rabbit subcutaneous connective tissue.
(Arrows shows a capillary vessel)

3. Discussion

It would be very important to clarify whether pulsatility of the blood flow is essential for the living body or not, because it would be the keypoint to develop the future artificial heart. One of the effective methods to prove it is to observe the microcirculation chronically and continuously without restriction of the behavior such as anesthesia. The authors have been developing an implantable probe to observe the microcirculation using a CCD camera. However, many obstacles such as pixel number of CCD, magnification and resolution of the micro-lens, focusing mechanism, light source and the total size of the probe had to be overcome. Magnification and the probe size were almost satisfactory to be implanted. The problems are associated with development of the micro focus mechanism and the illumination method. The micro-focus mechanism is being developed using a shape memory alloy. Our final goal is to observe the microcirculation not only at the thin and soft tissue like connective tissue but also at the parenchymatous organs such as the lung, kidney, liver, etc. For this purpose, it would be important to find out what kind of light (wave length, brightness, transmission or reflect, etc) should be projected.

4. Conclusions

Many types of implantable probes to observe the microcirculation were designed and evaluated. Although several problems such as the micro focus mechanism, light source and the resolution remain unsolved, its possibility to be completed in the nearest future has been proved.

References

1. Imachi K., Asano M., Fujimasa I., Sakurai Y., Atsumi K.: Micro-circulation in rabbit ear chamber during artificial heart pumping, *Digest of 10th Intern. Conf. on Med. and Biolog. Eng.*, 1973, 137.
2. Imachi K., Chinzei T., Abe Y., Isoyama T., Mabuchi K., Imanishi K., Ono T., Kouno A., Kusakabe M., Atsumi K., Fujimasa I.: A new apparatus for chronic observation of microcirculation in-situ to evaluate an artificial organ performance. *ASAIO Journal*, 1994, 40(3), M757–761.
3. Imachi K., Abe Y., Chinzei T., Mabuchi K., Imanishi K., Isoyama T., Kouno A., Ono T., Fujimasa I.: Factors Influencing hemodynamics blood chemical data and hormone secretion of total artificial heart goat. In: *Progress in Microcirculation Research*, H. Niimi, M. Oda, T. Sawada, R-J Xiu (Eds), Pergamon Press, London, 1994, 453–458.
4. Imachi K., Chinzei T., Abe Y., Isoyama T., Mabuchi K., Imanishi K., Ono T., Kouno A., Kusakabe M., Onuma M., Atsumi K., Fujimasa I.: Development of a new apparatus to observe the microcirculation chronically in a continuous flow blood pump research. *Artificial Organs*, 1995, 19(7), 723–728.
5. Imachi K., Chinzei T., Abe Y., Isoyama T., Mabuchi K., Imanishi K., Kusakabe M., Ohnuma M., Fujimasa I.: A new method for the chronic evaluation of the microcirculation during artificial heart pumping. In *Heart Replacement-Artificial Heart 5*, T. Akutsu, H. Koyanagi (Eds), Springer-Verlag, Tokyo, 1996, 281–287.

Nanotechnology in Artificial Organ Development and its Application in Diagnosis Methodology in Baroreflex Sensitivity of Patients with Hypertension

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Space in the human body is so limited that nanotechnology and micromachining technology are important for development of the internal artificial organs. Based on nanotechnology, development of various kinds of artificial organ has been conducted in Tohoku University, including artificial myocardium, artificial heart, rotary blood pump, artificial esophagus and artificial sphincter. Furthermore, automatic control algorithm for the artificial heart and assisted circulation was applied in the invention of the new diagnosis methodology for the baroreflex sensitivity of patients with hypertension. A successful clinical application of this new invention was made. Technical application of the large range of the developments is expectable in artificial internal-organs development.

Key words: nanotechnology, artificial myocardium, rotary blood pump, baroreflex sensitivity, hypertension

1. Introduction

From the historical point of view, miniaturization of artificial internal organs has been one of the most important factors until now. Space in the human body is so limited that nanotechnology and micromachining technology are important in development of the internal artificial organs. Based on nanotechnology, various artificial organs have been developed in Tohoku University, including artificial myocardium, the artificial heart, the rotary blood pump, the artificial esophagus and artificial sphincter. These various artificial internal organs are based on the common base technology. Biocompatible nano materials are important. Transcutaneous energy transmission

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systems using nanotechnology are also an important factor. In this paper, the recent progress of the artificial internal organ development is reported. Furthermore, automatic control algorithm for the artificial heart and assisted circulation was applied to the invention of the new diagnosis methodology for the baroreflex sensitivity of patients with hypertension. A successful clinical application of this new invention was performed. Technical application of the artificial internal-organ developments is expectable.

2. Artificial Internal Organs Using Nanotechnology

Based on nanotechnology, development various artificial organs has been performed in Tohoku University, the including artificial myocardium, the artificial heart, the rotary blood pump, the artificial esophagus and artificial sphincter.

2.1. Artificial Esophagus

Everybody knows that surgery of esophageal cancer is difficult because of the reconstruction of the esophagus after the resection of the carcinoma tissue. If there is an artificial esophagus, surgery will be simple and easy. Surgery with artificial esophagus will be feasible with only fiberscope.

In Tohoku University, the project on the artificial esophagus is ongoing [1]. Based on the achievements of the project, invention of the therapeutic stent, which has a therapeutic effect on the carcinoma tissue and the drinking function, is now under development. This therapeutic and drinking stent is easily inserted into the esophagus without any invasion. So this therapeutic and drinking stent was easily used for patients with the end stage esophageal cancer, which is not respectable.

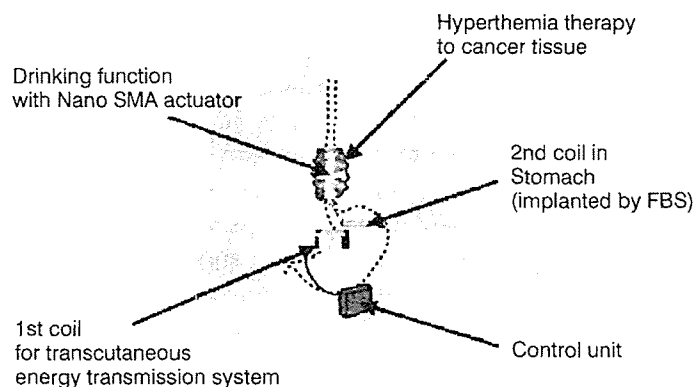


Fig. 1. Therapeutic and drinking stent for the end stage esophageal cancer

2.2. Artificial Myocardium

The final place which should be assisted is the myocardial contraction after a complete surgical repair. Even after complete revascularization of the coronary artery and a complete repair of the heart valve, cardiac output cannot be maintained when the contraction power is insufficient. An artificial myocardium system was invented in Tohoku University by the use of nanotechnology [2]. This system consists of various kinds of nanotechnology units, including the surface finishing technology, several kinds of nano sensors, nano microtip PC, and TETS with nano tech.

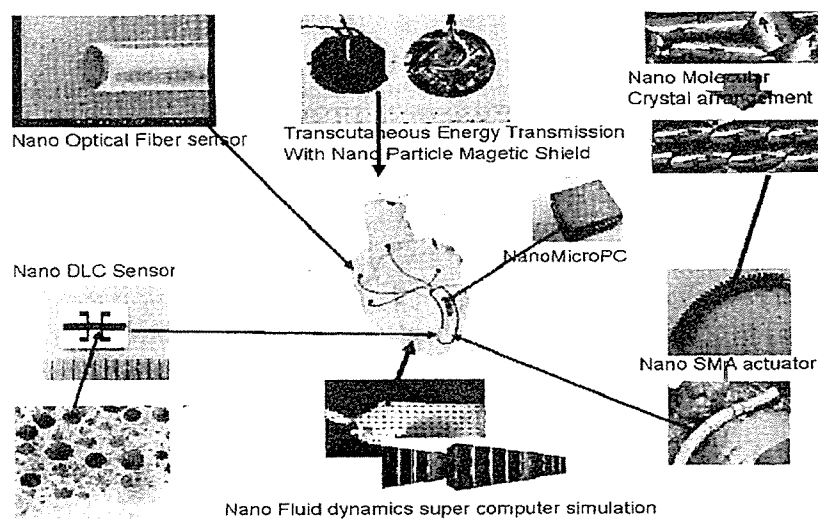


Fig. 2. Artificial myocardium

2.3. Artificial Heart

By the use of nanotechnology, an artificial heart system using the Undulation Pump system has been developed in Tohoku University. This system consists of various kinds of nanotechnology items, including surface finishing technology, several kinds of nano sensors, nano microtip PC, and TETS with nano tech. The control logic for the artificial heart and the artificial myocardium needed the system identification, so this logic might be useful for the diagnosis of the circulatory condition of the patients.

3. Baroreflex Sensitivity of the Artery in the Patients with Hypertension

A system identification is required for the automatic control of the artificial heart and the artificial myocardium. The system identification is useful for the diagnosis of patients with circulatory diseases.

Metabolic syndrome attracts attention as an important pathophysiology item in Japan [3]. Hypertension is one of the important elements which constitute the Metabolic syndrome. In a healthy human body, even if the blood pressure rises, the heartbeat decreases reflectively, the blood vessel relaxes and the blood pressure is lowered. However, this reflective function fails in the hypertensive patient [4–5]. It is known that the baroreflex function is insufficient or weak especially in the case of youth hypertension [6–7].

In order to diagnose the function of baroreflex, there are some diagnostic methods. For example, there is the method of calculating from the reaction of the heartbeat to blood-pressure change. No method of diagnosing the baroreflex function of a blood vessel existed at all.

We invented the first method of diagnosing the baroreflex function of a blood vessel. This new diagnostic method is outlined in this paper. The equipment which diagnoses the baroreflex function of a blood vessel does not exist in all in the world. This is because the method of measuring the elasticity of a blood vessel by the noninvasive method is difficult. Then, we paid our attention to the pulse wave transmission time (PTT) and the pulse wave velocity (PWV).

PTT and PWV are dependent on the elasticity of the arterial wall. According to the increase of the arterial wall elasticity, PWV will become increased. This phenomenon was applied, and the methodology which measures the baroreflex function of a blood vessel was invented from PWV information. The conceptual diagram of the system is shown below.

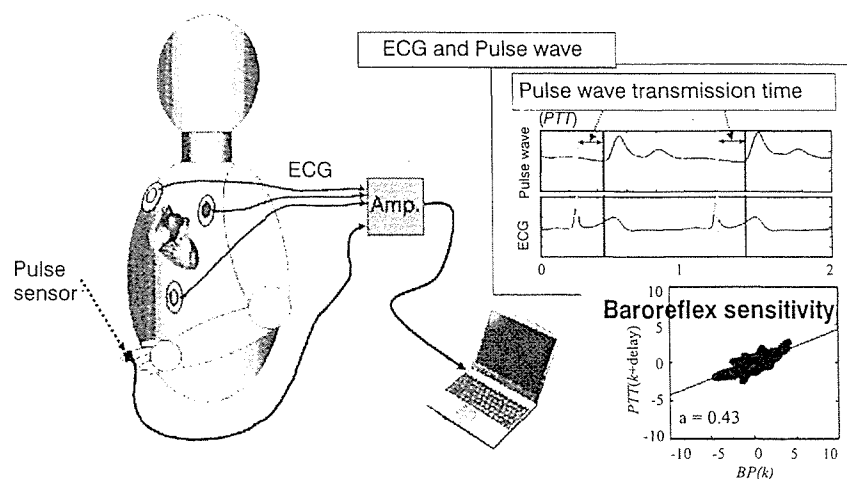


Fig. 3. Baroreflex sensitivity evaluating system

In this system, the measurement parts are only the pulse wave and the electrocardiogram. Cardiophonogram may be used for substitution of the electrocardiogram. The arm, the wrist, or the ankle are sufficient as the measurement part of the pulse wave. The data will become exact if loads, such as conversion of the posture and injection of the medicine, are added. Diagnostic measurement is possible even if there is no load.

The acquired time series information is input into a personal computer through an AD converter. Quantification and statistics processing are calculated. The time series of the cardiac contraction is measured from the R wave of the electrocardiogram or two sound of the cardiophonogram. The RR interval is changed into the Y-axis. The wave by which the smoothing was carried out by the Spline interpolation is re-sampled in 200 ms. As for the digital data, by which the discrete sampling was carried out, the frequency analysis is performed. Fluctuation of each time series curve is calculated. The delay time with the greatest correlation is calculated from the cross-correlation of the obtained time series. By this means, the influence that a change of blood pressure produces on the elasticity of the blood vessel will be calculated. The X axis is set as the change of the blood pressure, and the Y-axis is set as PWV or PTT after the delay time with the greatest correlation. The regression straight line is computed using the method of the least square. The methodology which adds a band pass filter to the time series curve and enables to observe the Mayer wave around 0.1 Hz is sufficient.

An example of the cross-correlation of the systolic blood pressure time series and the pulse wave transmission time series is shown in Fig.4.

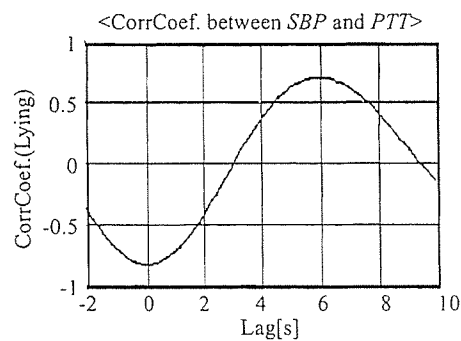


Fig. 4. Cross correlation of the SBP and PTT

In this example, the greatest cross-correlation in the delay time around about 6.0 seconds is observed. Then the pulse wave transmission time after the blood-pressure change and the delay time of the maximum correlation was plotted.

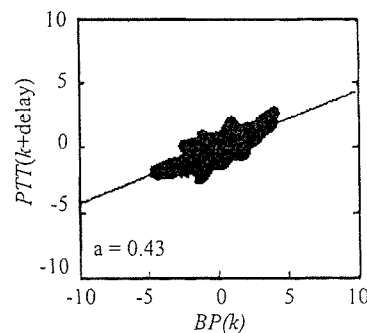


Fig. 5. Baroreflex sensitivity of the artery

The result by which a significant correlation was observed showed that blood-pressure change changed the blood vessel elasticity, reflectively. The regression straight line was calculated by the method of the least square. The sensitivity of the baroreflex function of the blood vessel can be calculated from this result. In the case in which the blood pressure is high, the baroreflex function of the blood vessel showed a falling tendency.

Previously the method of calculation of the baroreflex function of a blood vessel did not exist. We invented the method of calculation of the baroreflex function of the blood vessel from information processing of the blood pressure and the pulse-wave propagation time. The correlation analysis showed a changing PTT according to the blood-pressure change after several seconds.

From the regression straight line, it is expected that the sensitivity of the reflective function of the blood pressure is calculable. From now on, collection of cases can be performed after their examination by the Ethics Committee of the appropriate hospital.

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References

1. Watanabe M., Sekine K., Hori Y., Shiraishi Y., Maeda T., Honma D., Mryata G., Saijo Y., Yambe T.: Artificial esophagus with peristaltic movement. *ASAIO J.* 2005 Mar-Apr, 51(2), 158–161.
2. Yambe T., Shiraishi Y., Yoshizawa M., Tanaka A., Abe K., Sato F., Matsuki H., Esashi M., Haga Y., Maruyama S., Takagi T., Luo Y., Okamoto E., Kubo Y., Osaka M., Nanka S., Saijo Y., Mibiki Y., Yamaguchi T., Shibata M., Nitta S.: Artificial myocardium with an artificial baroreflex system using nano technology. *Biomed. Pharmacother.* 2003 Oct, 57 Suppl. 1, 122–125.
3. Matsuzawa Y.: The metabolic syndrome and adipocytokines. *FEBS Lett.* 2006 May 22, 580(12), 2917–21. Epub. 2006 Apr 21. Review.
4. Beske S.D., Alvarez G.E., Ballard T.P., Davy K.P.: Reduced cardiovascular baroreflex gain in visceral obesity: implications for the metabolic syndrome. *Am. J. Physiol. Heart Circ. Physiol.* 2002 Feb., 282(2), H630–635.
5. Pikkujamsa S.M., Huikuri H.V., Airaksinen K.E., Rantala A.O., Kauma H., Lilja M., Savolainen M.J., Kesaniemi Y.A.: Heart rate variability and baroreflex sensitivity in hypertensive subjects with and without metabolic features of insulin resistance syndrome. *Am. J. Hypertens.* 1998 May, 11(5), 523–531.
6. Honzikova N., Novakova Z., Zavadna 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), 237–242.
7. Lipsitz L.A., Iloputaife I., Gagnon M., Kiely D.K., Serrador J.M.: Enhanced vasoreactivity and its response to antihypertensive therapy in hypertensive elderly women. *Hypertension.* 2006 Mar, 47(3), 377–383.

DEVELOPMENT OF AN ARTIFICIAL MYOCARDIAL ASSIST DEVICE USING A SOPHISTICATED SHAPE MEMORY ALLOY FIBRE (BIOMETAL)

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The authors have been developing a mechano-electric artificial myocardial assist system (artificial myocardium) which is capable of supporting natural contractile functions from the outside of the ventricle without blood contacting surface. In this study, a nano-tech covalent type shape memory alloy fibre (Biometal, Toki Corp, Japan) was employed and the parallel-link structured myocardial assist device was developed. And basic characteristics of the system were examined in a mechanical circulatory system as well as in animal experiments using goats. The contractile functions were evaluated with the mock circulatory system that simulated systemic circulation with a silicone left ventricular model and an aortic afterload. Hemodynamic performance was also examined in goats. Prior to the measurement, the artificial myocardial assist device was installed into the goat's thoracic cavity and attached onto the ventricular wall. As a result, the system could be installed successfully without severe complications related to the heating, and the aortic flow rate was increased by 23% and the systolic left ventricular pressure was elevated by 6% under the low cardiac output condition at 2.5L/min in a goat. Therefore it was indicated that the effective assistance might be achieved by the contraction by Joule heating of the system using Biometal.