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Original paper

Non-linear dynamic analysis of hemodynamic parameters in an undulation type artificial heart system

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Abstract

Undulation pump total artificial heart (UPTAH) is a unique total artificial heart implant (TAH) using an undulation pump that is a continuous blood flow pump. To evaluate the autonomic nerve function mediating the circulation system, we analyzed the hemodynamic parameters during animal experiments with UPTAH using the non-linear mathematical analyzing technique, including chaos and fractal theory. Adult female goats were used for the implantation of UPTAH. The natural heart was replaced with UPTAH under extra-corporal circulation. The conductance- and arterial pressure-based control method (1/R control) was applied on the 5th to 7th post-operative day as the influences of the cardiopulmonary bypass circulation were diagnosed to be terminated. Hemodynamic parameters were recorded on the data recorder, and non-linear mathematical analysis was performed. For the quantitative evaluation of the strange attractor, which was the characteristics of the deterministic chaos, the fractal dimension analysis was carried out. As a result, hemodynamic parameters fluctuated on the time axis and showed fractal characteristics, which were thought to be the characteristics of the deterministic chaos. The reconstructed attractor of the hemodynamics showed various behaviors according to changes in the situation of the goats. These results suggest that non-linear dynamical analysis might be useful in monitoring the circulatory regulatory system in artificial heart circulation.

Keywords: Undulation pump; Total artificial heart; Chaos; Fractal; UPTAH

1. Introduction

The undulation pump total artificial heart (UPTAH) [1], which was developed at the University of Tokyo, is a small size total artificial heart implant using an undulation pump that is a continuous blood flow pump (Fig. 1). The driving mechanism and flow pattern of UPTAH is so unique that we examine the circulatory regulatory system using UPTAH. In this paper, to evaluate the circulatory regulatory system including the artificial heart under various conditions, a non-linear mathematical analyzing technique including chaos and fractal theory [2-9] was used on the UPTAH implanted animal.

2. Material and methods

Adult female goats weighing between 40 and 79 kg were used for the implantation of UPTAH. Under general anesthesia, the left chest cavity was opened with a fifth rib resection. The natural heart was replaced with UPTAH under extra-corporal circulation [10]. After surgery, the cardiac output was maintained at 100 mL/kg/min by controlling the right pump manually. To prevent lung edema,

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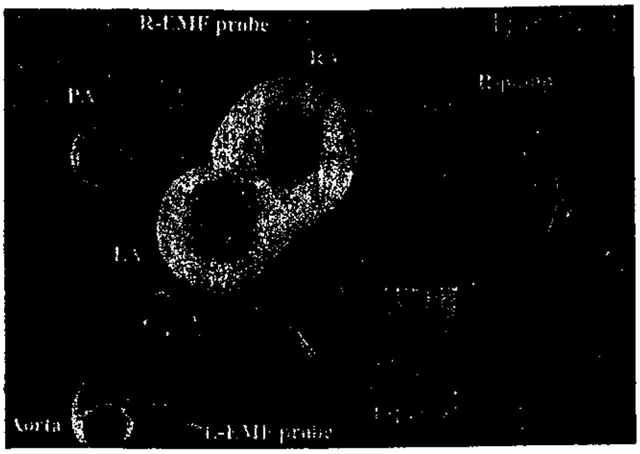

Fig. 1. A photograph of an undulation pump total artificial heart (UPTAH). R-EMF probe: right electromagnetic flow probe; RA: right atrium; PA: pulmonary artery; LA: Left atrium; L-EMF probe: left electromagnetic flow probe; R pump: right pump; L pump: Left pump.

the left atrial pressure was controlled automatically around 8mmHg. The arterial pressure-based control method (1/R control) [10,11] was applied on the 5th to 7th post-operative day.

During experiments, aortic blood pressure, pulmonary arterial pressure and left and right atrial pressures were continuously monitored via fluid filled catheters with pressure transducers (Nihon Koden, Tokyo, Japan). Left and right pump outputs were continuously measured with electromagnetic flow probes (Nihon Koden). Time series data of hemodynamic parameters were embedded into the phase space and projected into the three dimensional phase space. For the quantitative evaluation of the reconstructed attractor, fractal dimension analysis of the reconstructed attractor [2-5] was carried out using a personal computer system.

3. Results

To date, 47 cases of implantation have been performed on adult goats, and 1/R control has been applied in 10 cases. The longest survival of a UPTAH goat was 81 days. Recorded hemodynamic parameters were analyzed in the computer system once the conditions were stable. Time series data of pump output, blood pressure and left atrial pressure waveform are shown in Fig. 2. Unfortunately, some time series waveforms were significantly influenced by the body position of the experimental goats, and some spikes were observed in the blood pressure waveform, probably because of influences of the body motion to the fluid filled catheter. We therefore used the waveform of the left pump output in this study.

For example, the reconstructed attractor of the left pump output waveform, embedded into the four dimensional phase space and projected into the three dimensional phase space, is shown in Fig. 3. The larger shape attractors are shown during the sitting position compared to standing, although the band of the attractors did narrow a little.

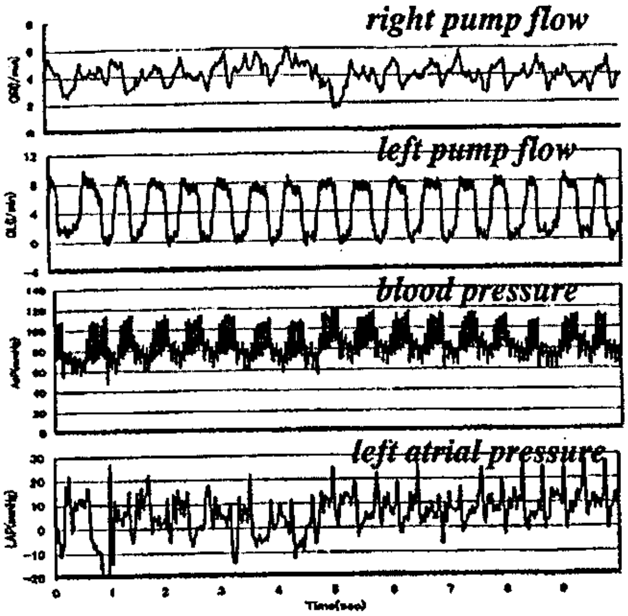

Fig. 2. Time series data of the hemodynamic parameters in a goat fitted with UPTAH.
QR: right pump outflow; QL: left pump outflow; AoP: aortic pressure. LAP: left atrial pressure.

As shown in the altered pattern in this figure, the shapes of the attractors were significantly altered with the behavior of the goats. Quantitative evaluation was attempted in this study using the fractal dimensional analysis of the reconstructed strange attractors, which had fractal characteristics. For example, the fractal dimension of the left pump output tended to decrease when the goats was standing, suggesting a change in the circulatory regulatory system. However, because of large standard deviations, no significant tendency of the changes in the fractal dimension were observed with each behavior of the goats.

4. Discussion

In this study, UPTAH was implanted in normal adult goats and a normal circulation was obtained. Hemodynamic parameters with UPTAH showed various circulatory behaviors according to changes in the condition of the experimental goats. These changes may be due to the properties of peripheral vessels mediated by the autonomic nervous system and some hormonal mediators.

It was interesting to note that the shape of the strange attractors was altered during the sitting and standing positions. Some reports have showed that the parasympathetic nervous system tends to increase during sitting or resting [2-7]. These investigators reported the increase of the

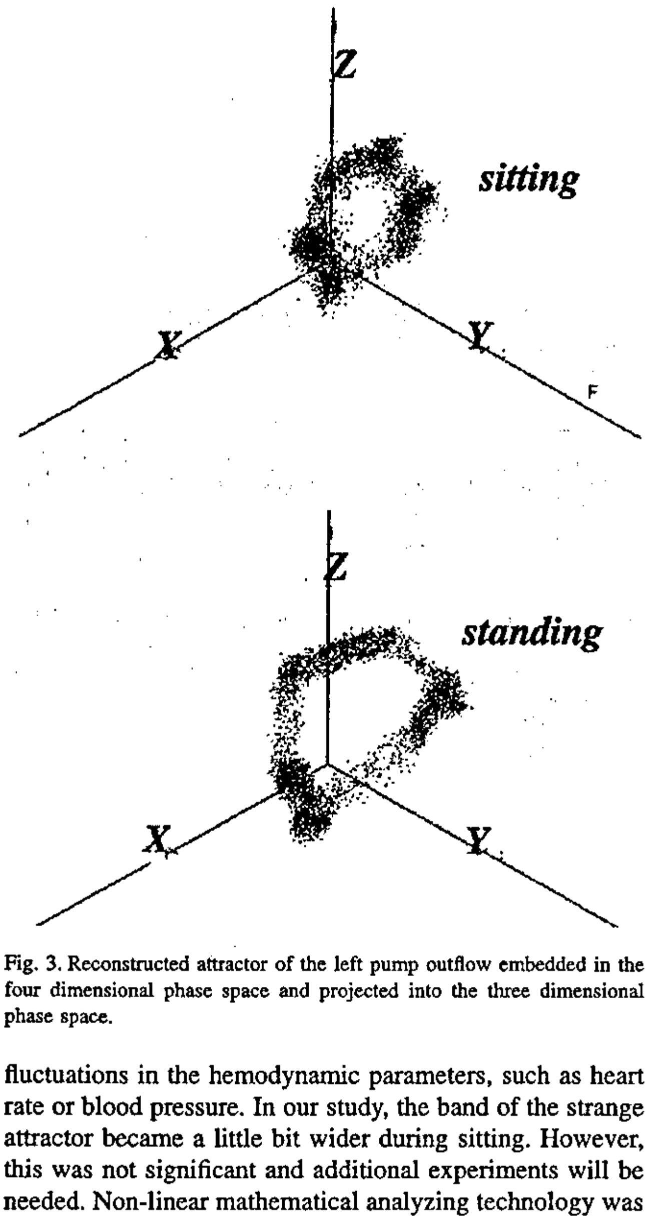

Fig. 3. Reconstructed attractor of the left pump outflow embedded in the four dimensional phase space and projected into the three dimensional phase space.

fluctuations in the hemodynamic parameters, such as heart rate or blood pressure. In our study, the band of the strange attractor became a little bit wider during sitting. However, this was not significant and additional experiments will be needed. Non-linear mathematical analyzing technology was very sensitive to the condition of the various parameters. It depended on an autonomic nervous system, hormonal factors, body motion, mental condition of the goats, and so on. A lot of parameters influenced the non-linear dynamics in the cardiovascular system and it was very difficult to evaluate the non-linear dynamic behavior quantitatively. However, this technique was so sensitive that it might be useful for the evaluation of cardiovascular dynamics in artificial heart circulation, including UPTAH.

As shown in Fig. 3, the shape of the attractors changed according to the condition of the goats, suggesting that these methodologies may be useful for the monitoring of the circulatory regulatory systems (including the autonomic nervous system), which are responsible for the chaotic dynamics of the hemodynamic parameters.

Of course, further investigation is needed. We will continue these approaches aiming at the sensitive monitoring methodology of artificial circulation.

Acknowledgements

The mathematical methodology of this paper was discussed in the workshop "Various approaches to the complex systems" held at the International Institute for Advanced Studies.

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Artificial Baroreflex System Makes Deterministic Chaos

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ABSTRACT

Biomedical-engineering research was chosen as the 21st century COE by governmental selection in Tohoku University. This COE team is due to develop various biomedical-engineering researches, so that artificial organ development especially using nanotechnology is performed. There are the various controlling methods in various artificial hearts. We invented the control system common to all artificial circulation equipments. A control system is important for maintenance of homeostasis. There is no baroreflex system in an artificial heart. We developed the control system which imitated the baroreflex for the artificial heart. First, the mathematical model was created. In the mathematical model, if time lag is short, blood pressure will be converged on a fixed value. However, if time lag is long, blood pressure will not become a fixed value but will be oscillated. Furthermore, blood pressure became chaos when time lag was long. We confirmed this result by animal experiments. The experiment was conducted by the animal experiment of full bypass circulation with RP. As a result, circulation without a pulse was also possible for the baroreflex by our resistance based adaptive control (RBAC) system. And hemodynamics showed fluctuation, even during nonpulsatile circulation. The application to a present still newer artificial circulation system is under plan. The implantable type artificial myocardium plan is progressing in Tohoku University, making full use of the latest nanotechnology. Into artificial myocardium, it is due to be equipped with the baroreflex control with a nano sensor and a nano computer chip. Arrival of the society which does not die of cardiovascular diseases is desired by the newest artificial myocardium.

Key words: 21st century COE in Tohoku University, artificial baroreflex system, artificial heart, ventricular assist divice, deterministic chaos

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INTRODUCTION

Biomedical-engineering research was chosen as the 21st century COE by governmental selection in Tohoku University. This COE team is due to develop various Biomedical-Engineering researches. In Tohoku University, research and development of an artificial organ have been done from dozens of years before.[1-5] The first clinical success case in Japan of a ventricular assist device was acquired in Tohoku University Hospital. The medical treatment examination headquarters of the ventricular assist device of Nippon Zeon was assigned in Tohoku University (Fig. 1).

Recently, various artificial organs are developed.[6-10] The 21st century COE program of Tohoku University thinks artificial organ development as important. Artificial organ development especially using nanotechnology is performed.

In Tohoku University, the sensor for living bodies with the structure of nano level is developed. Since this sensor is excellent in durability, it is the best for an artificial organ. We have succeeded also in development of the control chip computer of micro level. In the combination of a nano sensor and a microchip computer, a nano baroreflex system takes shape.

The cell structure of a living body is micron level. If it succeeds in the baroreflex system development of nano level structure, the cell structure of a living body will be exceeded.

The 21st century COE program promotes the nano biotechnology research which exceeds the function of a living body. Therefore, development of a nano artificial baroreflex system is tried in this study.

VARIOUS ARTIFICIAL HEART AND VARIOUS AUTOMATIC CONTROL ALGORITHM

In a hospital, various artificial organs are used for the various purpose.[1-10] Various artificial circulation equipments are developed. It is roughly divided into a total artificial heart and a ventricular assist device. A total artificial heart replaces the natural heart after surgical removal (Fig. 2). Therefore, a total artificial heart is asked for a perfect performance.

On the other hand, a ventricular assist device is equipment with which circulation is assisted. Various circulation assist devices have been developed until now.

The system which can be used easily is desirable in the emergency spot. Percutaneous cardiopulmonary support system (PCPS) is easy and useful. Circulation is maintainable from an emergency unit to an operating room. However, PCPS cannot be used for a long time. A thrombus tends to adhere to artificial lungs and a rotary pump. Prolonged use of PCPS is dangerous. There are many patients whom circulation does not recover in a short time. The assist device which can be used more for a long time is required for such a

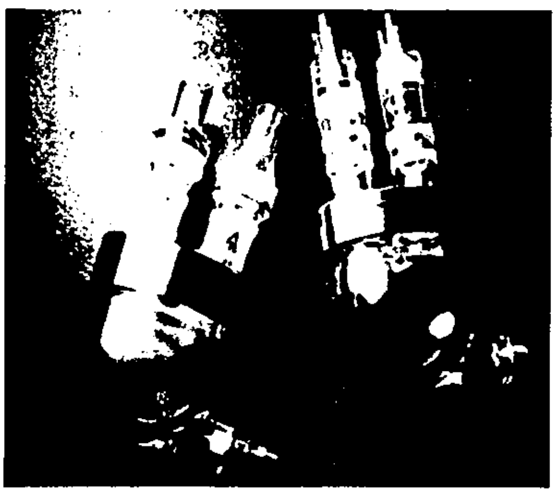

Fig. 1 Nippon Zeon ventricular assist device developed in Tohoku University.

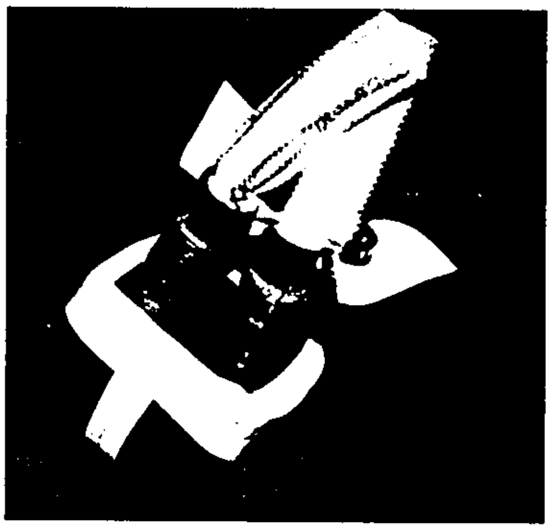

Fig. 2 Pneumatic driven total artificial heart developed in Tohoku University.

patient.

In Japan, the ventricular assist device of an air pressure drive is used for such the patient (Fig. 1). When using air pressure drive type equipment, it is not separated from a driving gear by the patient. Substantially, a patient becomes bedridden in ICU.

For the quality of life (QOL), a complete-implantable type is desirable. Now, many implantable type ventricular assist devices are developed overseas. However, the artificial heart developed in Europe and America is too large.

Small VAD is desired for Japanese people.

In order to miniaturize, there is also a method using rotary blood pump (RP).[11,12] However, a pulse is lost in RP. Then, we made frequency increase. If frequency is made to increase, the chamber will be made small. Then, a small artificial heart can be made. And it is also a capacity type blood pump. Therefore, a pulse can be made easily. This is the major candidate of a small artificial heart.

The new methodology to which frequency is made to increase using rotation had developed. It is the new artificial heart called undulation pump artificial heart (UPAH). Undulation movement is changed into pump movement in this artificial heart (Fig. 3). Now, a total artificial heart is manufactured and it is used for the animal experiment.

Moreover, we had made the artificial myocadium.

In this system, a machine pushes the heart. It is the same as the heart massage in the emergency spot. Therefore, the validity of a principle is established. We used the ball screw type electromagnetic motor (Fig. 4). It is the same principle as the robot arm of a space shuttle. Therefore, it excels in durability. Small auxiliary circulation is attained by this.

Thus, there are various artificial hearts. Various artificial hearts are used for the various purpose. There are the various controlling methods in various artificial hearts. However, it is the same at the point of maintaining circulation. Then, a common control algorithm is needed. We invented the control system common to all artificial circulation equipments.

ARTIFICAL BAROREFLEX SYSTEM

A control system is important for maintenance of homeostasis. The baroreflex system is one of the typical things of homeostasis. In human's body, if blood pressure goes up, a heart rate will fall. Since a heart rate falls, a cardiac output falls. Blood pressure will become low if a cardiac output decreases. Therefore, blood pressure is maintained by the fixed range. This is the main action of a baroreflex system.

However, there is no baroreflex system in an artificial heart.[13-16] Even if blood pressure goes up, a heart rate does not change. Therefore, hypertension is maintained. With the artificial heart research institution in the world, high blood pressure has occurred to the animal with an artificial heart. Therefore, it is thought

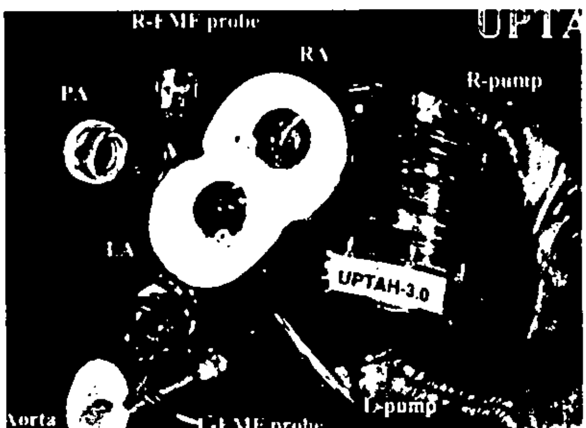

Fig. 3 Totally implantable undulation type artificial heart system.

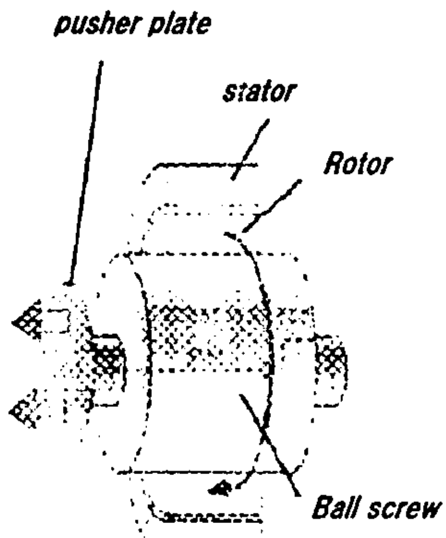

Fig. 4 Electromagnetic motor of a ball screw type for an implantable artificial myocardium.

that a baroreflex is required for an artificial heart.

We developed the control system which imitated the baroreflex for the artificial heart. The animal experiment was conducted with the mathematics simulation and the hydraulics simulation. Consequently, the validity of baroreflex control was proved.

MATHEMATICAL SIMULATION OF AN ARTIFICAL BAROREFLEX SYSTEM

First, the mathematical model was created.

Windkessel model was used for the model of left-heart circulation. This is the typical model which many researchers have used.[17-19] We added the baroreflex system to this famous model (Fig. 5). If blood pressure goes up, control to which a cardiac output decreases will be added. Human's body holds nonlinearity. Then, nonlinearity was introduced into this relationship. For that purpose, a sigmoid curve is used. Furthermore, as for an important thing, there is time lag in human's control system. Even if disturbance is added, it will take time, before a reaction from the control system comes out. Therefore, time lag is required for the simulation of a control system.

The simulation showed the interesting result. A result changes with values of time lag. If time lag is short, blood pressure will be converged on a fixed value. It was the result of showing classic homeostasis.

However, if time lag is long, blood pressure will not become a fixed value but will be oscillated. Furthermore, blood pressure became chaos when time lag was long.

This was a surprising result. Time lag had played the role important for generating of chaos.

We confirmed this result by other experiment systems.

ANIMAL EXPERIMENT SHOW THE UNIVERSALITY OF THE ARTIFICIAL BAROREFLEX SYSTEM

It was applicable to all artificial hearts. It was applicable to RP and PCPS. The baroreflex which reacts even if there is no pulse was a surprising research result. Human's baroreflex is because it happens for a pulse.

A receptor for a baroreflex system in human body generates a signal in the portion of the standup of a pulse. Many researchers have reported this phenomenon. Therefore, baroreflex control of a living thing cannot be performed without a pulse. RBAC control does not necessarily need a pulse, if information is inputted. It is the automatic control system which exceeds a life phenomenon in a sense.

Is such a thing truly possible?

We showed the result. The experiment was conducted by the animal experiment of full bypass circulation with RP. The heart was electrically fibrillated, and all

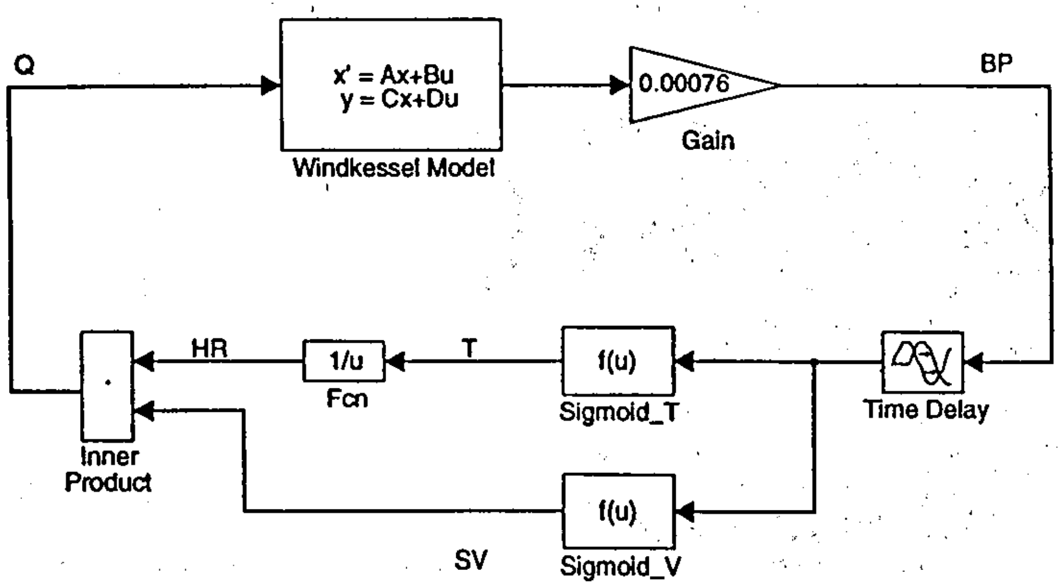

Fig. 5 Block diagram of the mathematical model of a baroreflex system.

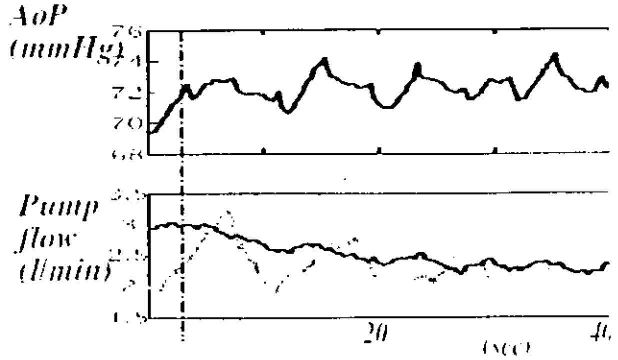

Fig. 6 Time series data of the total nonpulsatile circulation with a baroreflex system during drug administration.

circulation was maintained only by RP. Therefore, there was no pulse.

However, baroreflex control was possible as shown in Fig. 6. Fluctuation of a hemodynamics was observed in the figure. When blood pressure was changed with the medicine, the automatic control system reacted. Blood pressure returned by the automatic control system.

As a result, circulation without a pulse was also possible for the baroreflex by our RBAC system.

It is also an interesting result that fluctuation occurred although there is no pulse. The circulation in which human beings do not have a pulse has not been experienced. Therefore, it is not known whether there is any fluctuation by the artificial heart without a pulse. Now, RP is used as an assisted circulation by clinical. However, a total artificial heart is not made into non-pulsation by clinical. There was little research done non-pulsation by the total artificial heart.

Fluctuation was discovered by perfect non-pulsation circulation by this research. This fluctuation is the very interesting result of being in agreement also with a mathematical model.

These results may be able to be called surprising.

The baroreflex impossible for all lives without a pulse became possible. The life which had a baroreflex system without a pulse for the first time on the earth was born.

Furthermore, it was the result of bringing a new view to the possibilities of RP. For the miniaturization of an artificial heart, RP is absolutely advantageous. Since a pumping chamber is not needed, it is only a rotary motor. The problem was that there is no pulse. If there is no pulse, autonomic control in a life will not be performed. Also physiologically, it was a problem.

RBAC control may be able to solve this problem. When human's body needs, a circulatory state must change. Our control can respond to this change. Therefore, the life excellent in QOL is attained. Because we can catch up the need of your body.

The application to a present still newer artificial circulation system is under plan. It is the artificial myocardium plan which received the research cost of 120 million from the Ministry of Health, Labor and Welfare. The present implantable type artificial myocardium plan is progressing in Tohoku University, making full use of the latest nanotechnology.

Into artificial myocardium, it is due to be equipped with the baroreflex control with a nano sensor and a nano computer chip. Arrival of the society which does not die of cardiovascular diseases is desired by the newest artificial myocardium.

This paper was presented in part at 6th Congress of Clinical Application of Chaos Analyzing Methodology Meeting in Kanazawa, Japan. The authors thank Mr. Kimio Kikuchi for experimental preparation and kind cooperation, Miss Yoko Ito, and Mrs. Hisako Iijima for their excellent technical assistance and kind cooperation.

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ORIGINAL ARTICLE

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Akira Tanaka, PhD · Kenichi Abe, PhD
Hideki Takayasu, PhD · Makoto Yoshizawa, PhD
Hiroshi Takeda, PhD

Correlation dimension analysis of the artificial circulation

Abstract Artificial circulation has been analyzed by decomposing it into parts. However, the sum of the decomposed parts is not equal to the whole system, especially in nonlinear dynamic systems such as biological systems. To evaluate prosthetic circulation as an entity, not as decomposed parts, nonlinear mathematical analytic techniques, including fractal dimension analyzing theory, were used. Two pneumatically actuated ventricular assist devices were implanted as biventricular bypasses (BVB) in chronic animal experiments using four healthy adult goats. For comparison between natural and prosthetic circulation in the same experimental animals, the BVB-type complete prosthetic circulation model with ventricular fibrillation was adopted. All hemodynamic parameters with natural and prosthetic circulation were recorded under awake conditions and calculated by a personal computer system. By the use of nonlinear mathematical techniques, time-series data of the hemodynamics were embedded into the phase space, and correlation dimension analysis was performed to evaluate the reconstructed attractor. Our results suggest that the correlation dimension of the arterial blood pressure does not linearly increase according to the increase of the embedding dimension, even during artificial circulation, suggesting those are the fractal time series data. Dimensional analysis of the hemodynamics revealed that lower dimensional fractal dynamics were observed during prosthetic circulation. Fractal time series data are suggested to have robustness and error resistance. Thus, our results suggest that the circulatory regulatory system with the artificial heart may have these desirable characteristics.

Key words Chaos · Fractal · Fractal dimension · Total artificial heart · Correlation dimension

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Introduction

In 1981, Guevara et al. first reported that the cellular and subcellular mechanisms that produce the cardiac action potential were characterized by a chaotic attractor.[1] Other investigators reported that nonoscillatory cardiac tissues also manifested nonlinear dynamics.[2–4] Furthermore, the physiological function of the natural heart is characterized by a complex interaction of many control mechanisms that enable it to adapt to the changing environment.[5–7] This complexity, derived from the field of nonlinear dynamics, made it difficult to analyze the circulatory regulatory system quantitatively.[8,9] Analysis of nonlinear dynamics is currently an active field of research.[10,11] Its application to the cardiovascular system may aid our understanding of many physiological phenomena.[11]

Chaotic motion arises in nonlinear dynamic systems and can generate random-like time series, which closer analysis reveals to be highly ordered and critically dependent on the initial conditions.[2,12] Mathematically, all nonlinear dynamic systems with more than two degrees of freedom can generate deterministic chaos, becoming unpredictable.[2–4] To describe periodic, aperiodic, or even chaotic behavior of nonlinear systems arbitrarily with more degrees of freedom, several approaches have been applied.[2,13]

The concept of the *fractal* was developed by Mandelbrot to deal with complex geometric forms.[10,11,14] A fractal structure is not smooth and homogeneous. Instead, fractals are irregular, but their irregularity has an underlying pattern.[15,16] The more closely a fractal object is inspected, the more structure is revealed. Furthermore, the smaller-scale structure is similar to the larger-scale form.[15,16] Of physiological interest is the fractal-like branching structure of many anatomical structures, such as the central nervous system, vascular system, His-Purkinje fibers, and so on.[10]

Chaotic behavior in phase space generally has a *fractal dimension*,[10,14] a feature that allows its recognition. Periodic and quasiperiodic motions possess integer values;[2,10] however, chaotic motions have fractional values. The topological properties of the attractors and their quantification by dimensionality analysis may be an appropriate tool in the classification of circulatory dynamics and, thus, a possible diagnostic tool.[10,11] During the past decades, several investigators have undertaken nonlinear analysis using Grassberger and Procaccia's algorithm to evaluate the correlation dimension of time-series data.[17]

The use of the artificial heart has increased for the treatment of patients with severe heart failure following cardiac surgery and acute myocardial infarction. Thus, it is important to analyze the physiological effect of the artificial heart on the circulatory regulatory system.[18] In this study, to analyze the circulatory regulatory system with the artificial heart on an entity, not as decomposed into parts, the hemodynamic parameters of the artificial heart were analyzed by the correlation dimension analyzing technique that has been useful in the study of nonlinear dynamics coincident with deterministic chaos. Nonlinear behavior, such as chaotic dynamics, shows sensitive dependence on initial conditions; thus, use of the same experimental animals in the same conditions is desirable. For comparison between natural and artificial circulation in the same experimental animals, the biventricular assist-type total artificial circulation model under ventricular fibrillation in chronic animal experiments was adopted.

Materials and methods

Animal experiments

The experimental goats weighed 60 to 70kg, with a mean of 65kg. They were fasted for 2 days before the experiments. Three goats were anesthetized by halothane inhalation. After tracheal tube intubation by tracheotomy, they were placed on a respirator. Electrodes for the electrocardiogram (ECG) were attached to the legs and later implanted into the pericardium.

The left pleural cavity was opened by left fifth rib resection. Arterial blood pressure was monitored continuously with catheters inserted into the aorta through the left internal thoracic artery. Central venous pressure was measured by the fluid-filled catheter through the internal thoracic vein. For left artificial heart implantation, the intercostal arteries were separated to free the descending aorta. A polyvinyl chloride (PVC) outflow cannula was sutured to the descending aorta. A PVC inflow cannula was inserted into the left atrium through the left atrial appendage. Both cannulae were connected to our TH-7 pneumatically driven sac-type blood pump by the built-in valve connectors.[7] The PVC outflow cannula and the inflow cannulae were inserted into the pulmonary artery and the right atrium, respectively. Then, both cannulae were connected to the right pump. Pump output was measured by the electromagnetic flowmeter attached to the outflow-side cannulae.

A TH-7 pneumatically driven sac-type blood pump[7] was used to constitute a biventricular bypass (BVB)-type artifi-

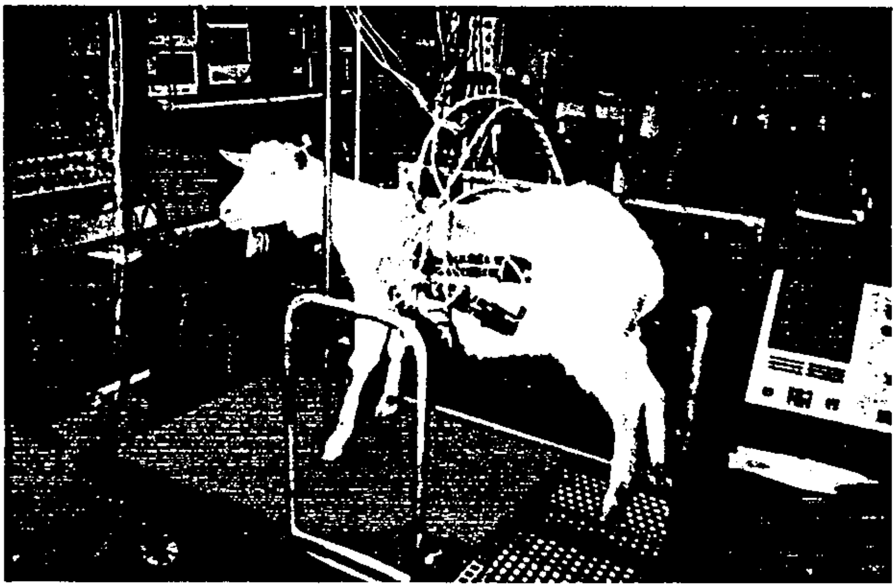

Fig. 1. Photograph of the goat with biventricular bypass type total prosthetic circulation model

cial heart model (Fig. 1). The inner sac of the pump was coated with polyurethane, and the outer casing of the pump was made of polycarbonate. Silicone ball values were affixed to the inflow and outflow connectors. Both blood pumps were driven by our newly developed pneumatic driving console.

After the chest was closed, these pumps were placed paracorporeally on the chest wall, and then the goat was placed in a cage and extubated after waking. After the influence of the anesthesia was thought to be terminated (2–3 days after the operation), the goat was intravenously heparinized (100 U/kg) to record the control time-series data without biventricular assist device driving. Data recording was performed under the awake condition, when the goat was standing and in preparandial condition. Time-series data of the hemodynamic variables were recorded with an ink-jet recorder and on magnetic tape, after stabilization of all hemodynamic derivatives without driving by the artificial heart (20–30 min after the biventricular assist devices were stopped).

After the recording of control data, bilateral ventricular assistance was started and ventricular fibrillation was induced electrically. Between 20 and 30 min after confirmation of stabilization of the hemodynamics during operation of the total artificial heart, time-series data of the hemodynamic variables were recorded. The driving condition of both pumps was manually operated to maintain a satisfactory pump output (80–100 ml/min/kg) and to maintain the hemodynamic parameters within normal limits. The driving conditions of both pumps were fixed when the time-series data of the hemodynamic parameters were recorded.

Dimensional analysis

The oldest concept of dimension is that of the topological dimension *Dt*. *Dt* is 0 for a point, 1 for a line, and 2 for a plane.[17] A first generalization is the fractal dimension or Hausdorff dimension. Chaotic dynamics in phase space generally has a fractal dimension, which allows its recognition. To discriminate between deterministic and random activity, one evaluates the dimension *D* of the attractors that have been constructed in the phase space. If we use the simple sets, for example, a limit cycle or torus, the fractal dimension is an integer and is equal to the topological dimension. Many physically feasible methods of defining dimension have been devised. They are classified into five categories[10]: changing coarse graining level, using the fractal measure relations, using the correlation function, using the distribution function, and using the power spectrum.

In this study, we used the correlation dimension analyzing technique by the Grassberger-Procaccia method, which is useful for the evaluation of high-dimensional complex systems.[19] By the use of these nonlinear mathematical methods, time-series data of the hemodynamic derivatives with the natural and artificial heart were reconstructed in the phase space.[2,20] The phase space is a useful concept for visualization of the system's dynamic behavior.[2–4] It is an abstract space whose coordinates are the degrees of freedom of the system being considered, i.e., the number of independent variables.[2,3,17] However, we cannot directly construct such a phase space for the circulatory regulatory system, which generates the hemodynamic time series data.

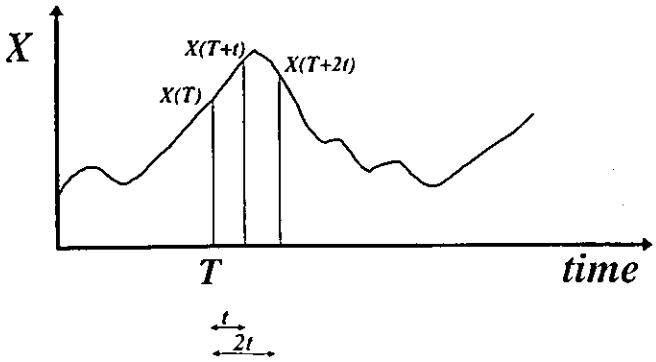

Fig. 2. Reconstruction methodology of the time-series data into phase space. The delayed values then define a single point in a multidimensional phase space and thus a vector (details shown in the text)

The first step is to find the phase space description of the digitized data. We had followed Taken's proposal and used the time-shift method.[20] In 1980s, Takens et al. proposed reconstructing the phase space by means of the time delay t. The values measured at fixed time delays $x(T), x(T+t), x(T+2t)$ . . . are treated as though they characterized new variables. The delayed values then define a single point in a multidimensional phase space and thus a vector (Fig. 2). If trajectories starting from different initial values are attached to a discrete region within the phase space with a lower dimension, this region is called an *attractor*. An attractor may have fractal dimension and is then called chaotic or strange.

To give a geometric explanation of the computation of the dimension, we will illustrate schematically a proposal made by Grassberger and Procaccia to compute the so-called correlation dimension *D2*. After reconstruction of the attractor in the phase space, the number of data points lying inside the circle that have a radius of $r^0, 2r^0, 3r^0, \ldots$ etc. is counted. When log (r) versus log $N(r)$, is plotted, a straight line is obtained. The slope of this line is exactly the dimension of the attractor.

By the use of these nonlinear mathematical methods, we calculated the correlation dimension of the hemodynamics during artificial circulation generated by the biventricular bypass pump under ventricular fibrillation, and compared it with that during natural heartbeat.

Results

A photograph of the complete artificial circulation model in the awake condition during the chronic animal experiment is shown in Fig. 1. After recording of control data without pump driving, ventricular fibrillation was electrically induced and the systemic circulation was maintained with the artificial heart.

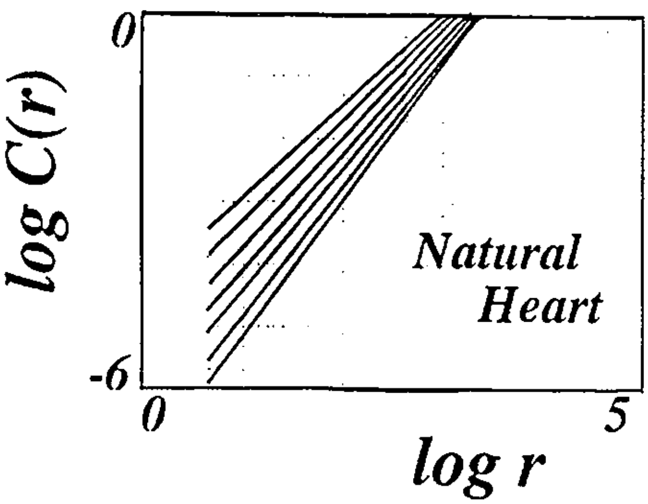

Fig. 3. Correlation dimension analysis of arterial blood pressure during natural heart beat without biventricular assistance (details shown in the text)

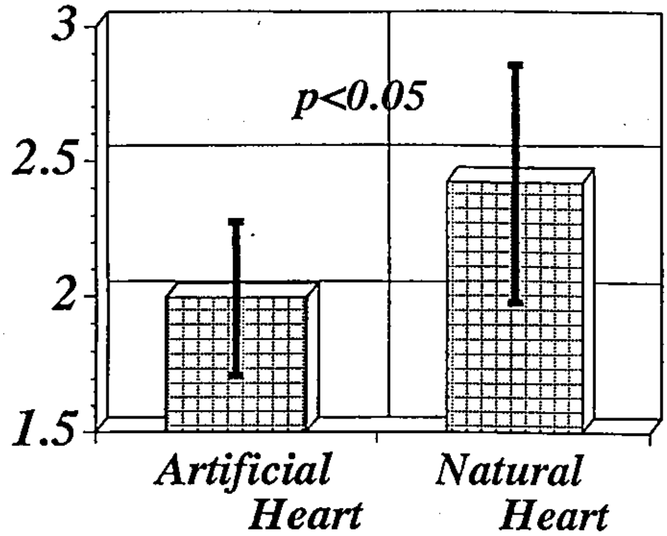

Fig. 5. Comparison of the correlation dimension (y axis) of arterial blood pressure during natural and prosthetic circulation in the same subjects by the use of the Grassberger-Procaccia dimensional analyzing algorithm

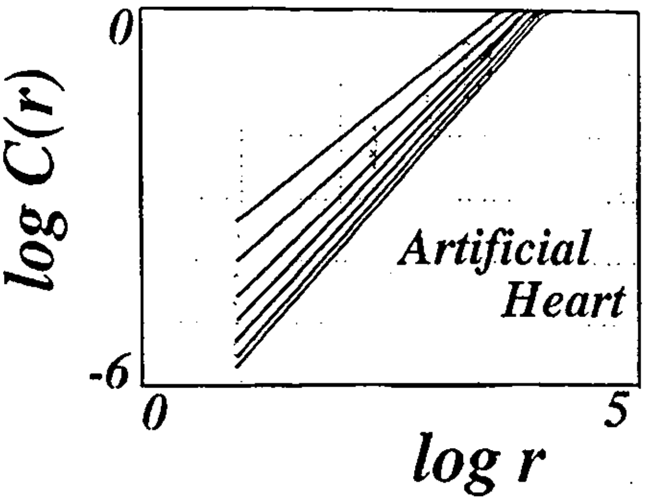

Fig. 4. Correlation dimension analysis of arterial blood pressure during complete prosthetic circulation with biventricular bypass pump

Satisfactory pump outputs (80–100 ml/kg/min) were easily obtained in this system, and all hemodynamic derivatives were easily controlled within normal values by manual control of positive pressure, negative pressure, systolic duration, and driving rate with the pneumatic drive console.

Fractal dimension analysis of arterial blood pressure was calculated in the computer by the correlation dimension analysis method using the Grassberger-Procaccia algorithm. For the dimensional analysis, time-series data of the hemodynamic parameters were embedded into the phase space by the nonlinear mathematical analyzing technique. As shown in Figs. 3 and 4, the slope was increased according to the increase of the embedding dimension from three to nine. However, increase of the slope showed the sigmoid pattern at its peak values. By the use of these peak values, we calculated the correlation dimension.

During natural heartbeat without assistance, the correlation dimension of the arterial blood pressure was 2.41 ± 0.44. Thus, the fractal dimension was significantly smaller than the embedding dimension and larger than 1, which is the dimension of the limit cycle attractor of a periodic system, suggesting that arterial blood pressure is the fractal time-series data. During operation of the artificial heart, the correlation dimension was 1.99 ± 0.28, significantly smaller than that obtained with time-series data of the hemodynamics with the natural heart ($P < 0.05$). The fractal dimension of arterial blood pressure during artificial circulation showed that time-series data of the hemodynamics had characteristics of fractals, even during prosthetic circulation.

Discussion

One of the major findings of this study is that the hemodynamics derivative was the fractal time-series data even during the artificial circulation produced by the pneumatically driven artificial heart. With the fractal time-series data, the slope of the relationship between log r and $N(r)$ does not linearly increase according to the increase in the embedding dimension.[19-21] The convergent values of this slope indicate the correlation dimension of the attractor.[19] With the random time-series data, the reconstructed attractor showed a nonstructured pattern, and the fractal dimension of this pattern is equal to the embedding dimension.[2-4] With the periodic data, the reconstructed attractor showed the characteristics of a limit cycle attractor, and its fractal dimension is 1.[2-4] Both the random and the periodic series are not fractal time-series data. The dimension of the fractal time-series data is a fraction and is significantly different from the dimension of both the random and the periodic time-series data.[10,14]

In summary, our data suggest that the time-series data of the hemodyamics during both natural and artificial circulation are fractal time-series data, because, first, the reconstructed attractor of the data plotting distribution in the phase space had fraction fractal dimension, and, second, their fractal dimensions were significantly different from that with a limit cycle attractor in a periodic system and that with a random distribution attractor. Several investigators have shown the robustness and error resistance of the fractal time-series data.[10,11,14] Thus, our results suggest that artificial circulation may show these desirable characteristics like those of natural circulation. Another finding of this study is that the fractal dimension of the hemodynamic derivatives with artificial circulation was significantly smaller than that with natural heart circulation. Our results show the possibility that the lower dimensional attractor was shown in the reconstructed attractor of the artificial circulation. A recent report from our team showed that rhythmic fluctuations of the hemodynamics were significantly changed during artificial circulation compared with natural circulation.[13] These phenomena must contribute to the fractal dimension of the hemodynamics with prosthetic circulation.

The fractal dimension revealed further information concerning the whole nonlinear dynamic system compared with conventional spectral analyzing methodology,[10,14] because power spectral analysis of the hemodynamics shows us the decomposed components of the circulatory regulatory systems, such as the sympathetic and parasympathetic nervous systems.[13] Deterministic analyses of the electrical signals appear to be more sensitive to changes in biological generators during normal function and abnormal pathology than the more common stochastic analyses.[21,22] These nonlinear mathematical analyzing techniques give us information concerning the whole circulatory regulatory system, and thus we can estimate the information entropy of the cardiovascular control system. From the viewpoint of the whole system, artificial circulation is mediated by the lower non-linear dynamic systems.

In conclusion, arterial blood pressure was fractal time-series data even during artificial circulation, and the fractal dimension of the hemodynamics during artificial circulation is smaller than that during natural circulation. These results suggest that artificial circulation has the characteristics of robustness and error resistance, and these nonlinear mathematical analyzing techniques give us information concerning the whole circulatory regulatory system, including the artificial heart.

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Open-loop Analysis of Transfer Characteristics from Blood Pressure to Heart Rate Using an Effectively Total Artificial Heart

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Abstract: It is desirable for the dynamic behavior of the drive rate of the artificial heart to be as similar as possible to that of the recipient's heart rate (HR) before implantation. This requires a model which can simulate the behavior of HR on the basis of only the information measured with the limited number of approvable implanted sensors. This article provides a linear time series model for explaining the behavior of HR only with aortic pressure and right atrial pressure. This could be obtained from open-loop analysis using a total artificial heart, which was introduced for measuring HR in vivo and for eliminating its effect on blood pressure. The model was identified in a goat equipped with a special biventricular assist device called the effectively total artificial heart (ETAH). The ETAH was introduced to make an open loop and awake situation in the animal with almost intact autonomic nerves, which could enhance the accuracy and reliability of the identification of the model. The adequacy of the proposed model was ascertained in several data sets measured in two goats, which were different from the data set used for identification. Most of the mean estimation errors were less than 3 beats/min and auto-correlation analysis showed approvable statistical appropriateness. However, it was clarified through comparison with the 1/R control method that the proposed model has a few problems still to be solved before its future implementation as an automatic controller of the TAH. **Key Words:** Heart rate variability—Total artificial heart—Peripheral vascular resistance—System identification—Autoregressive exogenous model.

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INTRODUCTION

One of the most important problems in controlling the total artificial heart (TAH) is how we should determine the cardiac output, i.e., the flow pumped out from the TAH to the vascular system. Although many methods for solving this problem have been proposed, no decisive methods have yet been found (1–4).

We may have two keys to solving this problem. One key is to clarify the total mechanism of the cardiovascular center determining the cardiac output. However, even if the mechanism is completely clarified, we will not be able to implement a controller with a similar mechanism because we can only measure a small part of the physiological information, while the cardiovascular center can use the whole information. The other key is to mimic the dynamic behavior of the cardiovascular center for regulating the cardiac output on the basis of the limited number of measurements that we can obtain in the realistic situation.

One of the simplest methods for simulating the dynamic behavior of the cardiovascular center is to create a controller so that the drive rate (DR) of the TAH can behave as similarly as possible to the recipient's heart rate (HR) on the basis of only the information measured with the limited number of approvable sensors. This requires a certain mathematical model which can express the dynamics of HR variability and an assumption that the stroke volume can be regarded as being constant.

The "1/R control method" proposed by Abe et al. (5) is a candidate of such mathematical models representing the behavior of the HR. In this method, the DR at the next step is determined as a function of the current DR, aortic pressure (AoP) and right atrial pressure (RAP), subject to a constant stroke volume regulated by an automatic controller. This method could achieve the long survival of animals equipped with TAHs driven by the fully automatic controller. However, the method requires a searching process of a control parameter depending on individual differences and external conditions, such as the response time of the pump output. This process prevents us from applying the method to clinical use because the process must be done in a trial and error manner.

The substantial feedback information used by the 1/R method must be included in the AoP and RAP. Thus, it may be possible to find another, better model which can simulate the dynamic behavior of the HR as a function of these pressures.

One of the simplest methods for finding such a model is to apply the system identification technique to the dynamic system from AoP and RAP to the HR. In the case of an awake animal or human, however, this identification is not easy because the cardiovascular system is a closed-loop system, i.e., the HR is fed back to vascular pressures. Theoretically, it is proved that we should make the closed-loop system open to identify its subsystems as accurately as possible (8,9). However, it will, of course, be difficult to directly cut the feedback loop, for example by blocking autonomic nerves, unless we introduce some special experimental conditions to maintain the subject's blood perfusion (8,9).

To realize an approximately open-loop situation, in this study, a special animal model equipped with a kind of biventricular bypass system, called an *effectively total artificial heart* (ETAH), has been introduced, as shown in the next section.

The ETAH can be expected to provide an accurate identification of the system from blood pressures to the HR because the ETAH enables us to observe the HR under conditions in which the HR has little effect on the blood pressure, in spite of an awake animal with an intact autonomic nervous system.

METHODS

Animal experiment

Figure 1 shows a schematic illustration of the animal experiment using the ETAH. Two pneumatically-driven blood pumps (TH-7, Tohoku University, Japan) were used as a biventricular bypass, withdrawing blood from the right and left atria and transfusing it to the pulmonary artery and the aorta, respectively. The right pump bypassed 100% of blood flow of the right ventricle and the left pump bypassed about 80% of that of the left ventricle by clamping the ascending aorta. Thus, the effect of the HR on blood pressure could be sufficiently reduced while the HR still remained because the coronary circulation was maintained by the rest, about 20%, of the systemic circulatory flow. This situation could be regarded as nearly open loop because the paths from the HR to blood pressures were nearly cut off. However, the HR was still determined by the cardiovascular center, depending on the artificial variation of blood pressures driven by the two blood pumps.

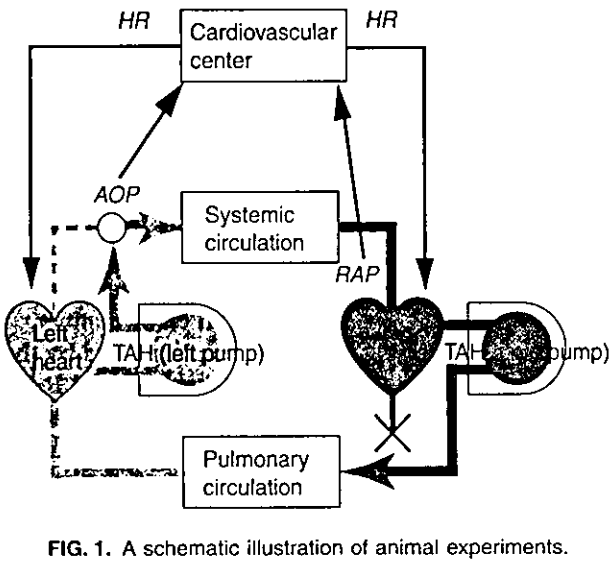

FIG. 1. A schematic illustration of animal experiments.

In the experiment, two adult goats were employed to apply the ETAH. The HR was obtained from ECG, measured with electrodes implanted at the pericardium. The AoP and RAP were measured using pressure transducers through fluid-filled side catheters at the outlet port of the left pump and the intake port of the right pump, respectively.

After implantation, the ETAH was manually controlled so that blood flow and pressure could be on roughly normal physiological levels. Because the circulation had been unstable immediately after the operation, data acquisition was started a week later. ECG, AoP, RAP and the drive signal of the ETAH were measured at 500 Hz on a personal computer with an A/D converter. The DR and HR were obtained from processing the drive signal and ECG, respectively. The AoP and RAP were averaged over a drive period of the ETAH, and their averaged values and the DR were recorded at every drive beat. Independent of these values, the HR was recorded at every natural heartbeat.

To keep the characteristic of the persistent excitation (10) for increasing identifiability, the DR was randomly changed according to a rectangular signal, as shown in Fig. 2(a).

Data processing and system identification

It is necessary to sample at a fixed rate to identify the system dynamics. Therefore, each beat-to-beat data series was resampled at 2 Hz after smoothing by means of the cubic spline function because the maximum drive rate was less than 120 bpm. Then the time series data was linearly detrended and normalized to have zero mean and unit variance.

To estimate coefficient parameters and delays, the cross-correlation coefficients between the AoP and the HR, and the RAP and the HR were calculated.

The model of the HR regulator was indicated as a general linear model. According to the general process of system identification, the autoregressive exogenous (ARX) model, which can be estimated easily, was selected as follows:

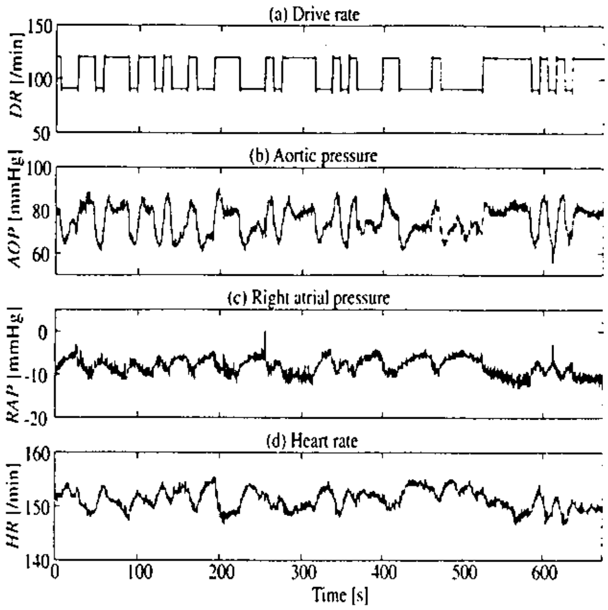

FIG. 2. The variation of *DR*, *AOP*, *RAP* and *HR* with time.

$$HR_k = \sum_{i=1}^{n} a_i HR_{k-i} + \sum_{j=0}^{m_{AOP}} b_j AOP_{k-L_{AOP}-j} + \sum_{l=0}^{m_{RAP}} c_l RAP_{k-L_{RAP}-l} + e_k \quad (1)$$

where HR_k, AOP_k and RAP_k are sampled values of the HR, AoP and RAP, respectively, and n, m_{AOP} and m_{RAP} are orders of HR_k, AOP_k and RAP_k, respectively. L_{AOP} and L_{RAP} are delays from AOP_k to HR_k and from RAP_k to HR_k, respectively. e_k is a residue.

First, L_{AOP} and L_{RAP} were determined from the first peak of the cross-correlation coefficient, and then all of the combinations in which the order of each parameter was from 1 to 10 were fitted to the data set with the chosen delays. The total number of models was 1000. For each of these models, the sum of the squared prediction errors and the resulting loss functions (normalized sum of the squared prediction errors) were computed. n, m_{AOP} and m_{RAP} were chosen such that the structure could have the smallest loss function.

Evaluation of identified models

To ascertain the adequacy of identified models, the output of the model was compared with measured data by using the following data sets.

A. The same data set as that used for the identification obtained from a goat.
B. Another data set obtained from the same goat as data set A in a different interval.
C. The data set obtained from another goat for which the DR was changed according to a random rectangular signal.
D. The data set obtained from the same goat as data set C for which the DR was kept constant.
E. The data set obtained from a goat not equipped with blood pumps but with only sensors, while 10 mg methoxamine hydrochloride was injected for changing blood pressure.

Data sets A and B were used to evaluate the adequacy of the parameter estimation. Data sets C–E were used to evaluate generality for individual differences. It is important to use data set E because the situation of the goats equipped with the ETAH may be very special.

If the system is correctly described, then the residuals associated with the data and a given model will ideally be white and independent of the input given to the model (10). To check these characteristics, the auto-correlation function of e_k and the cross-correlation function between e_k and the inputs, AOP_k and RAP_k, were computed.

RESULTS

Figure 2 shows an example of the time series data. It can be seen that the HR_k changed depending on variations of AOP_k and RAP_k caused by the change in DR_k. However, it can be considered that AOP_k and RAP_k were only slightly affected by HR_k because HR_k seemed to change to suppress the variation of these pressures, that is, HR_k increased with decreasing AOP_k and with increasing RAP_k, and vice versa. This implies that the baroreflex function of the cardiovascular center expressed in HR_k could work normally, even under almost the same condition as the TAH.

Figure 3(a,b) show the examples of the cross-correlation coefficients between AOP_k and HR_k and between RAP_k and HR_k, respectively. Note that HR_k is strongly correlated with AOP_k and RAP_k. The average lags at which the coefficients achieve their maximum are 5 s (the 10th sample) for AOP_k and 2.5 s (the 5th sample) for RAP_k.

As a result, L_{AOP} and L_{RAP} in Eq. 1 were chosen as follows:

$$L_{AOP} = 10, L_{RAP} = 5. \quad (2)$$

Then, after computing the loss function using Eq. 2, the orders of Eq. 1, n, m_{AOP} and m_{RAP}, were chosen as follows:

$$n = 2, m_{AOP} = 2, m_{RAP} = 2. \quad (3)$$

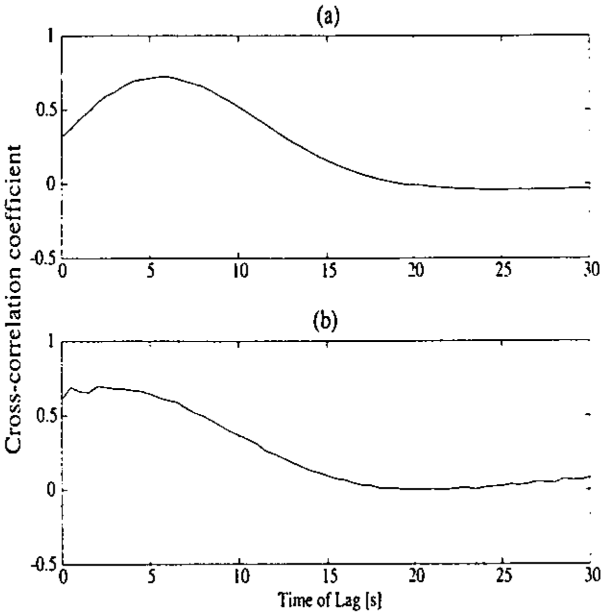

FIG. 3. The cross-correlation coefficient (a) from $-AOP_k$ to HR_k, and (b) from RAP_k to HR_k.

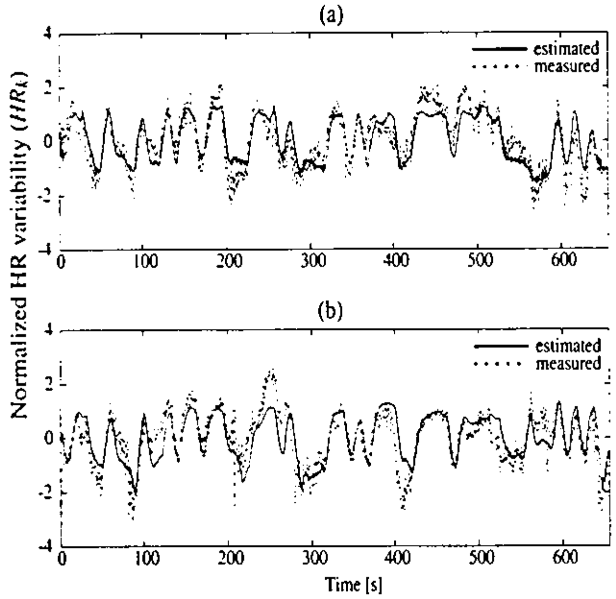

FIG. 4. The variation of the measured HR_k and its estimate for (a) data set A, and (b) data set B.

Finally, the parameters of the model were estimated using the least-squares method. Hence, Eq. 1 is expressed as follows:

$$HR_k = 0.32HR_{k-1} + 0.48HR_{k-2} - 0.19AOP_{k-10} - 0.08AOP_{k-11} + 0.10RAP_{k-6} + 0.02RAP_{k-7} + e_k. \quad (4)$$

Figure 4(a,b) show the variations of HR_k and its estimate with time. The estimates of Fig. 4(a,b) were calculated from data sets A and B, respectively. It can be seen that the linear model could estimate HR variability well, mainly at low frequencies up to the respiratory rate. The root-mean-squared value of the estimation error e_k was less than 2.0 beats/min.

Figure 5(a) shows the result of HR estimation in which the input data set was measured on a different goat from Fig. 4 (data set C). It can also be seen that the slow variation of HR is similar to the change in HR_k with AOP_k caused by the change in DR_k. The mean estimation error was less than 3.2 beats/min.

Figure 5(b) shows the result of the estimation in which the input data set was measured on the same goat as that of data set C but DR_k was kept constant (data set D). Hence, the change in AOP_k was not caused by the change in DR_k but in the characteristic of the systemic circulation and/or venous return. The estimation error was less than 3.1 beats/min.

Figure 6 shows the estimation results in which the input data set was measured on the different goat from Figs. 4 and 5, not equipped with blood pumps but with only sensors (data set E). In this data set, AOP_k was changed by injection of methoxamine hydrochloride (10 mg) at $t = 100$ s.

The auto-correlation function of e_k, the cross-correlation function between AOP_k and e_k, and the cross-correlation function between RAP_k and e_k are shown in Fig. 7(a,b,c), respectively. In each figure a 99% confidence interval, represented by dotted lines, is used to ensure that the residue e_k is indeed white and independent of the inputs. Almost all functions

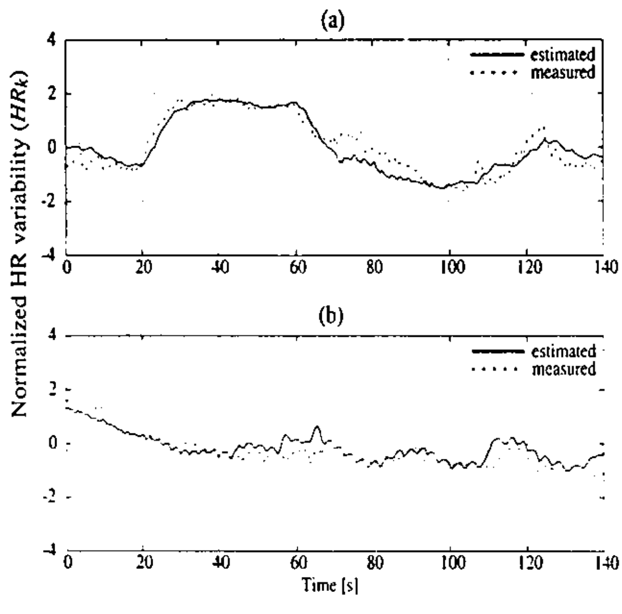

FIG. 5. The variation of the measured HR_k and its estimate for (a) data set C, and (b) data set D.

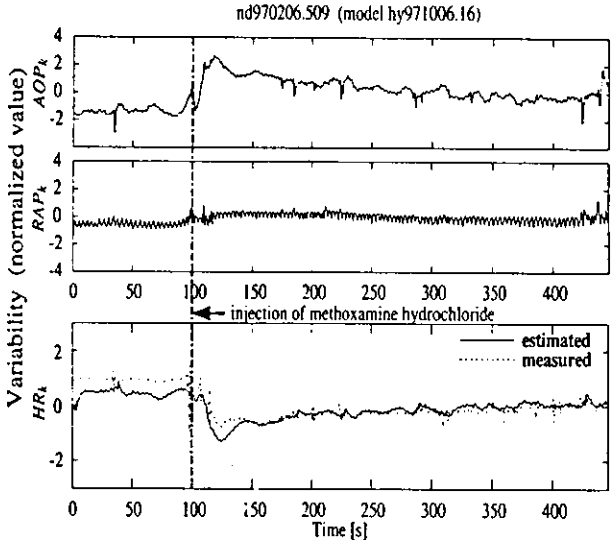

FIG. 6. The variation of the measured HR_k and its estimate based on data set E.

stay inside the interval, except for a few lag points. This result shows that the estimated model expressed by Eq. 4 may be statistically appropriate.

DISCUSSION

The present results of animal experiments have shown that the response of the HR to two kinds of blood pressures caused by the baroreflex function still remained under the awake and open-loop condition produced by the ETAH. Sugimachi et al. (8) and Kawada et al. (9) have already revealed the transfer function from the arterial pressure to the autonomic nervous activity under an open-loop condition in rabbits. However, these animals were anesthetized and their autonomic nerves were not perfectly intact. Moreover, the effect of preload was not considered because atrial pressure has never been analyzed.

As shown in Fig. 3, the values of the two delays, one is from the AoP to the HR and the other is from RAP, were different from each other. This suggests that the HR regulator has at least two control loops. One works depending on the afterload of the left heart and the other on the preload of the right heart. This indicated that the AoP and RAP should be fed back to the DR of the TAH with different delays rather than the same delay.

On the other hand, the 1/R control method manipulates the DR on the basis of the AoP and RAP with the same delay. Thus, the method leaves room for improvement, at least in adjusting delays in feedback loops.

The results of Figs. 4–6 mean that the identified ARX model could simulate the dynamic behavior of the HR at low frequencies up to respiratory rate, even in the three cases where the model was applied to different data sets obtained from the same goat, the different goat equipped with the ETAH and the different goat without the ETAH. Moreover, Fig. 6 suggests that it is possible to use the ARX model for estimating the HR to some extent on the basis of constant coefficient parameters, even when the peripheral vascular resistance is considerably changed.

This characteristic is important because it means that the functional relationship between blood pressures and the HR is roughly robust to the change in the peripheral vascular resistance and individual difference. It is a matter of course that this robustness is also desirable for general application of the automatic controller for the TAH because the structure or the parameters of the function determining the DR should be invariant for different hemodynamic states or different recipients.

As shown in Fig. 7, the results of the residual analysis showed statistical appropriateness of the identified ARX model. Thus, we cannot expect to improve the estimation accuracy any more as long as we use linear ARX models whose inputs are only the AoP and RAP.

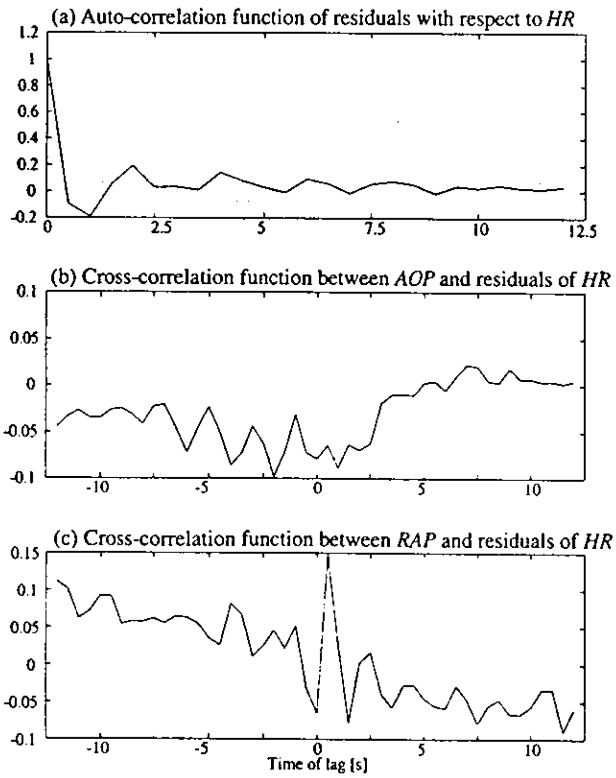

FIG. 7. The results of the residual analysis with respect to e_k.

However, this does not deny the existence of other better models with other additional kinds of inputs, for example, metabolic products (11) or the respiratory rate. In particular, the introduction of the respiratory rate may improve the estimation accuracy at high frequencies, which could not be estimated by the proposed model because it is well known that the HR variability has a high frequency component related to respiratory arrhythmia. However, its usefulness and significance are still unknown.

Furthermore, it may be impossible for the identified model to estimate a quick change in the HR caused by external factors such as emotion and mental stress, which are not directly related to blood pressure. However, this problem may not be so important for the achievement of long survival with the TAH at the present time.

If the sampling interval can be modified appropriately by interpolation using a linear or a spline function, then Eq. 4 will be able to be theoretically applied to TAHs as an automatic control algorithm. To implement such a controller in an actual implantable TAH, however, the following problems must be solved.

1. In the same way as the 1/R control method, use of blood pressure as input information is not suitable for the implantable and durable TAH because pressure sensors are apt to drift and have low bioadaptability.
2. Since Eq. 4 holds only for normalized data with zero mean and unit variance, it is necessary to calculate the mean values and the standard deviations of input and output signals every time when these values seem to change.
3. In the case of the 1/R control method, it can be predicted that the AoP and RAP will, if they can, converge to the corresponding setting points. However, Eq. 4 does not have such setting points or reference values of blood pressures.

CONCLUSION

To develop a new control algorithm of the cardiac output of the TAH, a linear time series model representing heart rate variability as a function of the aortic pressure and right atrial pressure was proposed. The model was identified in an open-loop situation produced by the effectively total artificial heart implanted in a goat. Hence, it can be expected that the reliability and accuracy of the identified model were sufficiently high. Furthermore, the model could estimate the dynamic variation of the heart rate of the different goat as well as the response which was obtained due to a drastic change in the peripheral vascular resistance caused by a drug administration. As mentioned in the Discussion, however, a few serious problems are still to be solved before implementing the proposed model as a practical automatic controller for the TAH.

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