別紙4

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Shiraishi Y, et al.	Morphological approach for the functional improvement of an artificial myocardial assist device using shape memory alloy fibres	Conf Proc IEEE Engineering in Medicine and Biology Society	2007	3974-3977	2007
Shiraishi Y, et al.	A newly-designed myocardial assist device using a sophisticated shape memory alloy fibre	Biocybernetics and Biomedical Engineering	27(1/2)	147-154	2007
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角張泰之，関根一光，佐藤文博，白石泰之，山家智之ほか	蠕動運動機能をもつ人工食道のための胃部留置型経皮的電力伝送装置の開発	生体医工学	45	PS2-3-5	2007
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August 23-26, 2007.

Morphological Approach for the Functional Improvement of an Artificial Myocardial Assist Device using Shape Memory Alloy Fibres

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A. Baba, S. Konno, S. Nitta, K. Imachi, K. Tabayashi, H. Sasada and D. Homma

Abstract— **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 15% and the systolic left ventricular pressure was elevated by 7% under the cardiac output condition of 3L/min in a goat. And those values were elevated by the improvement of the design which was capable of the natural morphological myocardial tissue streamlines. Therefore it was indicated that the effective assistance might be achieved by the contraction by the newly-designed artificial myocardial assist system using Biometal. Moreover it was suggested that the assistance gain might be obtained by the optimised configuration design along with the natural anatomical myocardial stream line.**

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I. Introduction

In general, the artificial ventricular assist systems, such as artificial hearts, were employed for the treatment of the severe heart failure in order to increase the circulation volume. However the complications caused by the hemolysis or thrombosis on the surface of the artificial materials are still outstanding problems in the application of those de-vices to patients. Heart transplantation has also been widely performed as destination therapy for the severe heart failure. But it is limited by donor organ shortages, selection criteria, as well as the cost [1]. And recently, cell transplantation to repair or supplement impaired heart tissue has been reported as an alternative therapy for that [2]. The authors assumed that the essence of the pathophysiological development of severe heart failure was in the decrease in the cardiac contractility. Then an artificial myocardium has been developed using a covalent nano-tech shape memory alloy fibre, which is capable of assisting natural cardiac contraction from out-side of the ventricular wall as shown in Figure 1 [3]. The purpose of this study was to develop a sophisticated artificial myocardium unit, and also to have examined the hemodynamic effects of the myocardial assist system on cardiac function.

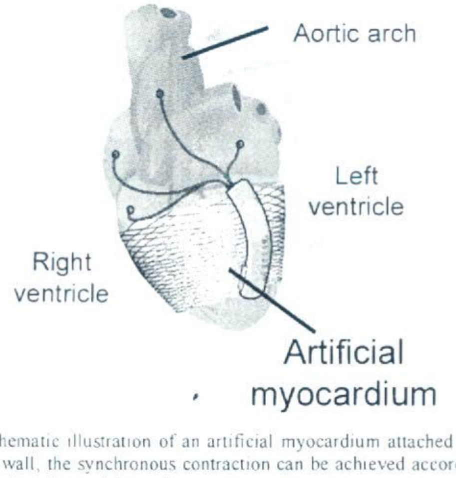

Fig. 1. Schematic illustration of an artificial myocardium attached on the ventricular wall, the synchronous contraction can be achieved according to the natural physiological demand.

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The authors have been developing a totally-implantable artificial myocardial assist device [4]-[6]. The methodologies of the direct ventricular support systems were already reported as direct mechanical ventricular assistance (DVMA) by Anstadt's or other groups, as well as the right ventricular assist device which was invented and reported at IDAC, Tohoku University [7]-[9]. In this study, a design to surround the total heart has been established in order to refrain from the stress concentration by the mechanical assistance, and the hemodynamic performance of the artificial myocardial assist system were examined in a mock circulatory system as well as on animal experiments using goats. And also morphological design approach has been conducted and basic characteristics of the three types of myocardial assist device were examined so that the representation of the anatomical structure of natural myocardial tissue for more sophisticated mechanical assistance from the outside could be achieved.

II. Materials and Methods

A. Artificial Myocardium using Shape Memory Alloy Fibres

The myocardial assist system, as shown in Figure 2, consists of a covalent type shape memory alloy fibre (Biometal®). The diameter of the fibre is 100 microns, and it is contracted by the Joule heating. In general, Ti-Ni alloy is well known as a material with the shape-memory effect[10]-[12]. The fibre material is able to be covered with a silicone –tubing (diameter: 150um). The configuration of the mate-rial was basically constructed by covalent bond, so that it indicated a big strain change by 5 to 10% in length. The linearity of the recovery strain and the changes in electric resistance could be adjusted through the fabrication process, so that the strain of the fibre could be easily controlled by using the digital-servo system without potentiometers.

The layered structures are formed in the ventricular wall from the anatomical point of view as shown in Figure 3, and the effective mechanical blood flow output is achieved by the integrative anisotropic contraction from epi- to endocardium [13].

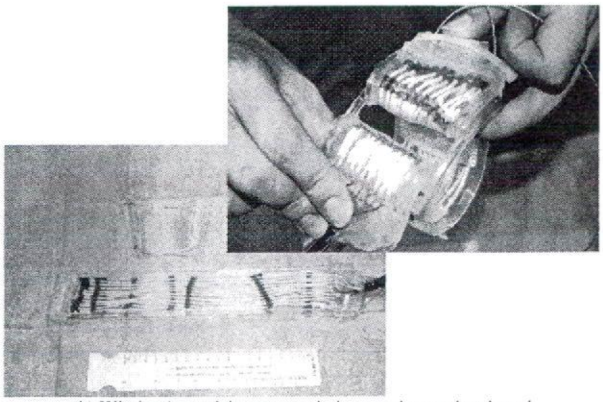
In this study, the authors developed a prototype artificial myocardium by using the shape memory alloy fibres for the simulation of such natural complicated myocardial tissue stream as shown in Figure 4. And the representation of the myocardial stream on the ventricular wall was performed by the oblique-shaped myocardial assist device.

B. Mock Circulatory Evaluation and Animal Experiments

Contractile function of the device developed was examined onto the originally-designed silicone mock left ventricle (Figure 3). Hydrodynamic evaluation was conducted against the afterload of 80 to 100mmHg without mock ventricular contraction.

Hemodyamic data were also obtained from normal adult

(a) Shape memory alloy fibre (D=100μm) covered with the silicone tubing



(b) Whole view of the myocardial assist device developed

Fig. 2: The mechanical component of the artificial myocardial actuator (a), and the myocardial assist device of parallel-link structure which was designed to be an active girdle for the ventricular contraction

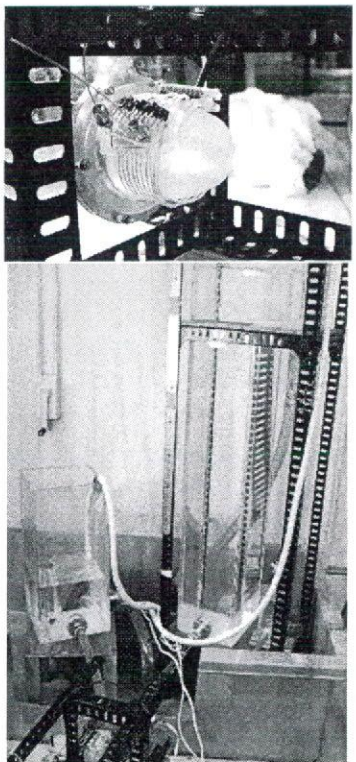


Fig. 3 Hydrodynamic examination of the artificial myocardium (top); the device was attached onto the silicone mock left ventricular model (bottom)

healthy goats, the mean weight of which was 50kg under the normal intubation and general anesthetizing process by 2.5% Fluothane. Prior to the measurement, the artificial myocardial assist device with parallel-linked shape memory alloy fibres was covered with silicone rubber, and it was attached onto the ventricular wall. Left ventricular (LV) pressure was measured by a catheter tip transducer (Millar, SVPC-664A), The sensor was inserted at the left atrial portion through the mitral valve. These hemodynamic data were recorded by a digital recording unit (TEAC, LX-10) and the sampling frequency was 0.5 - 1.5 kHz.

All the animal experiments related to this study were scrutinized and approved by the ethical committee on the animal experiment of the Department of Medicine, Tohoku University, and also the Institute of Development, Aging and Cancer, Tohoku University, 2004-2006.

III. Results and Discussion

A. Effects of the displacement on the ventricular contraction and design improvement by morphological representation

Basic contraction was achieved to be 5% shortening in each fibre module. Therefore the actual displacement for ventricular assistance together with the acrylic adjustment component was estimated to be over 7%, which was similar to the displacement change obtained from the goat's ventricular surface by using our 3D measurement [14].

As shown in Figure 5, the oblique type which was able to represent the natural morphological myocardial streamline indicated the bigger output of around 5L/min against the after load of 100mmHg in the mock circulatory system.

B. Surgical procedure and hemodynamic effects on the goat's cardiovascular system

In order to achieve the effective reduction of the volume inside of the heart during the systolic phase, the changes of the ventricular wall thickness might be inevitable. Though the concept of supporting cardiac function from outside by using this artificial myocardial assist system does not involve those native thickening function of the heart, the controllable displacement of this device might be useful for more sophisticated cardiac assist.

The myocardial assist device developed was successfully installed into the goat's thoracic cavity without any complications. Hemodynamic waveforms were changed by the mechanical assistance. It was not necessary to remove any costae to install the whole actuator into the thoracic cavity, whereas one rib should be taken away during the surgical procedure of the other electrohydraulic myocardial assist system which had been developed [6]. As the actuator employed for the artificial myocardium itself was so small, the less room in the thoracic cavity might be needed. Moreover,

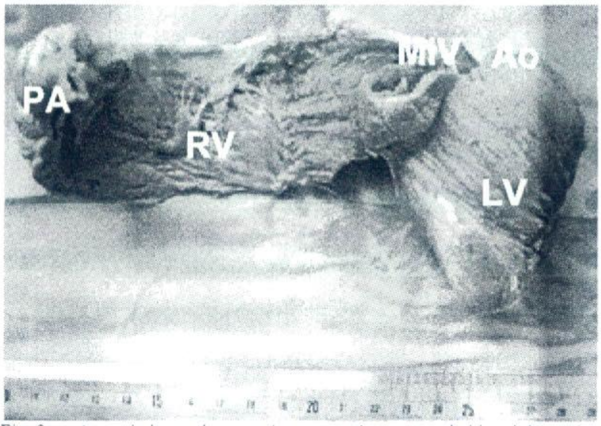


Fig 3 A goat's heart showing the ventricular myocardial band dissection which was unfolded by Torrent-Guasp's procedure

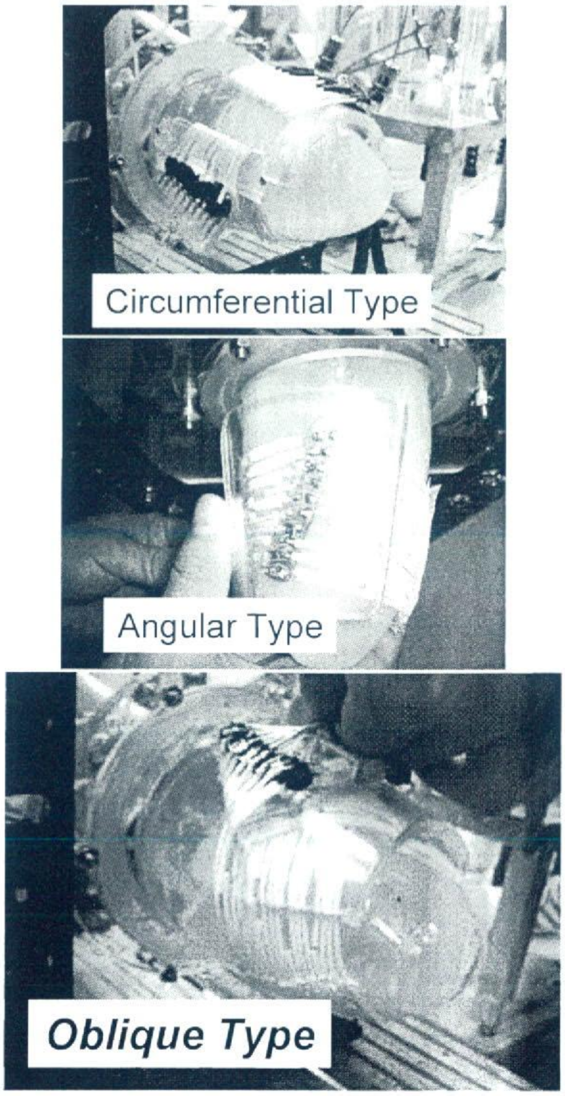


Fig 4: Three different types of the myocardial assist device developed: the oblique type at the bottom could represent the natural oblique stream of myocardial tissue around the left ventricle

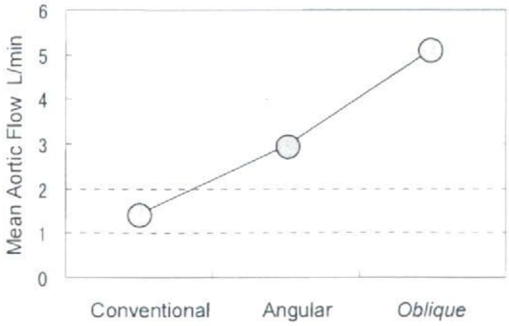


Fig. 5: Changes in mean aortic flow (ventricular model output) obtained from the mechanical circulatory system by using three different configuration types of myocardial assist device

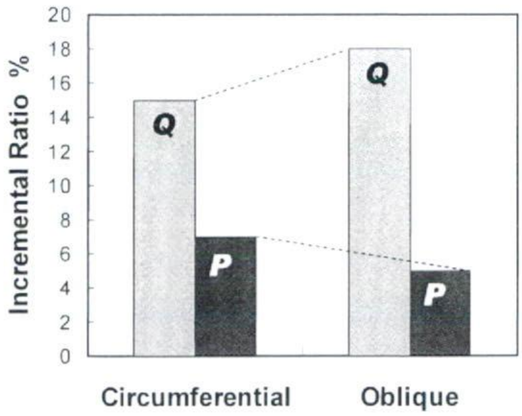


Fig. 6: Changes in the incremental ratio of the hemodynamic data with assistance, P: aortic systolic pressure, Q: aortic flow

the surgical procedure might be simpler compared with other ventricular assist systems. And also the complications, such as thrombosis or hemolysis, would not be caused by this myocardial assist device.

The aortic flow rate was increased by 15% and the systolic left ventricular pressure was elevated by 7% under the cardiac output condition of 3L/min by using the conventional circumferential type. And consequently, the incremental ratio of the left ventricular output was elevated to 18% by using the newly-designed oblique type as showin in Figure 6.

However, any other complications which might have been caused by the operation, such as the disorder of natural autonomic nervous system, were not confirmed in goats yet. As the remarkable increase of the hemodynamic data could be obtained, it was suggested that the effective assistance might be achieved by using this artificial myocardium.

IV. Conclusion

The improvement of an artificial myocardium using the sophisticated covalent shape memory alloy fibres was achieved, which was capable of being installed into the thoracic cavity as the epicardial actuator. As the load of this myocardial system, which was generated by the natural cardiac function, could be estimated by measuring the electrical resistance of the shape-memory alloy fiber, the mechanical myocardial assistance might be effective for heart failure conditions according to the cardiovascular physiological demand.

As our system could assist natural ventricular functions with physiological demand, it might be applied in patients with exertional heart stroke, as well as the cardiac massage at lifesaving emergency for the recovery from ventricular fibrillation.

Acknowledgment

The authors would like to extend their appreciation to Mr. K. Kikuchi and Mr. T. Kumagai for their cooperation in the experiments.

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A Newly-designed Myocardial Assist Device Using a Sophisticated Shape Memory Alloy Fibre

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Recently, the ventricular assist devices are widely applied for a surgical treatment of the final stage of severe heart failure as the bridge to heart transplantation or the destination therapy. However, it was anticipated that the artificial components in the ventricular assist devices might cause the problems concerning thrombosis and infection. As heart failure involves the decrease in myocardial contractile function, the mechanical assistance by using an artificial myocardium might be effective. In this study, the authors developed a mechano-electric artificial myocardial assist system (artificial myocardium), which is capable of supporting natural contractile function from the outside of the ventricle.

K e y w o r d s: shape memory alloy fibre, heart failure, cardiac assist device, hemodynamics

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1. Introduction

In general, patients with severe heart failure, who present an increased ventricular filling pressure or insufficient amount of blood supply to the tissue, are given medical or surgical treatment. Recently, artificial circulatory assistance by using ventricular assist devices, such as artificial hearts, has been provide, which is followed by heart transplantation. However, the deficiency of donor hearts might be a serious problem in the world. And the transplantation waiting period in this country extends to several years. Therefore, necessity of clinical application of artificial hearts with long-term durability has arisen. As the size of the western ventricular assist devices, which are provided at present, is still big for the smaller body size Asian people, several artificial heart projects are being conducted in Japan, and one of these has started clinical trials.

There are also some devices or procedures suggested to be useful for the surgical treatment of severe heart failure, such as the ventricular CorCup, Myosprint or Dor's procedure. And recently, cell transplantation to repair or supplement the impaired heart tissue has been reported on as an alternative therapy for that [2]. There are many problems about the tissue reproduced *in vitro* or *in vivo* that are not yet solved. Moreover, any control of the implanted tissue might be impossible from the outside.

As the heart failure is caused by a decrease in the myocardial contractile function, the direct mechanical myocardial assistance in response to physiological deficit, i.e. a synchronous support of the contractile function from outside of the heart, might be effective. The purpose of this study was to develop an artificial myocardium, which would be capable of supporting the cardiac contraction directly by using the shape memory alloy fibre of a minute diameter based on nano-technology.

The authors have been developing a totally-implantable artificial myocardial assist device [3–6]. The methodologies of the direct ventricular support systems were already reported on as direct mechanical ventricular assistance (DVMA) by Anstadt's or other groups, as well as the right ventricular assist device, which was invented and reported on at IDAC, Tohoku University [7–9]. In this study, the authors developed a prototype system of the mechano-electric artificial myocardium by using a parallel-linked covalent shape memory alloy fibres, which was shown in Fig. 1, and its basic hemodynamic performance was examined in goat experiments.

2. Materials and Methods

(1) Basic characteristics of the fibre and design of the artificial myocardium

In general, Ti-Ni alloy is well-known as a material with the shape-memory effect [10–16]. The fibre material (Biometal, Toki Corporation), which was used in this study for the development of artificial myocardium, has the configuration of

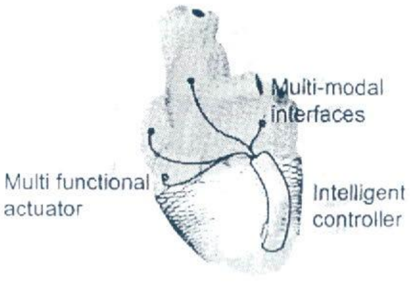

Fig. 1. Schematic illustration of a concept of the newly-designed artificial myocardium using a shape memory alloy fibre

a covalent bond, and demonstrates a marked strain change as shown in Fig. 2, which is similar to the changes in the surface strain in natural ventricle [17]. The linearity of the recovery strain and the changes in electric resistance could be adjusted through the fabrication process, so that the strain of the fibre could be easily controlled by using the digital-servo system without potentiometers.

The basic stress-strain characteristics were examined in a test circuit as shown in Fig. 3. Tensile force which was generated by the fibre and its displacement were measured simultaneously by a force transducer (Kyowa, LUR-A-50SA1) and a laser position sensor (Keyence, LB-01), respectively.

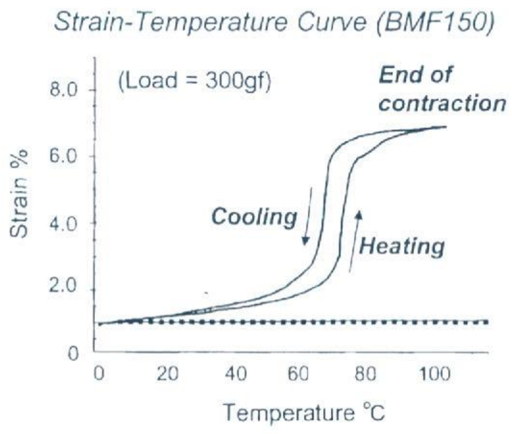

Fig. 2. Typical relationship between strain and temperature obtained from the Biometal fibre (diameter: 150 μm). Because of the linearity between the strain and the electric resistance, the displacement can be controlled by the simple circuit and also the sense of force can be estimated

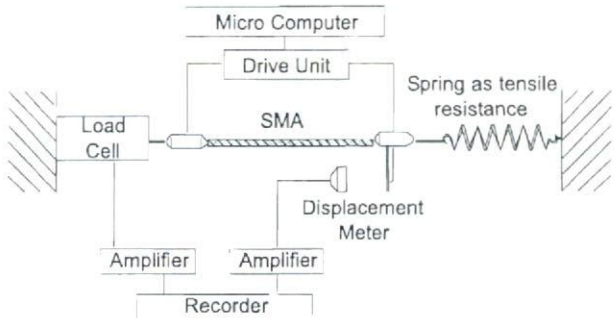

Fig. 3. Schematic drawing of the measurement system for the stress-strain characteristics of the shape memory alloy fibre. The spring constant as the tensile resistance was selected from 1.7 to 4.1 N/mm

The newly-developed electro-mechanical artificial myocardium consists of the following components: a) an actuator which was made of parallel-linked shape memory alloy fibres, b) an originally-designed signal controller. The weight of each fibre was 14 mg, and the length was set to be 280 mm. The total weight of the whole actuator was around 15 g. The myocardial actuator shown in Fig. 4 was attached onto the heart, and it could support the natural contractile function from the outside of the ventricular wall. Its mechanical assistive motion was synchronized with the electrocardiogram so as not to obstruct the natural cardiac diastolic functions.

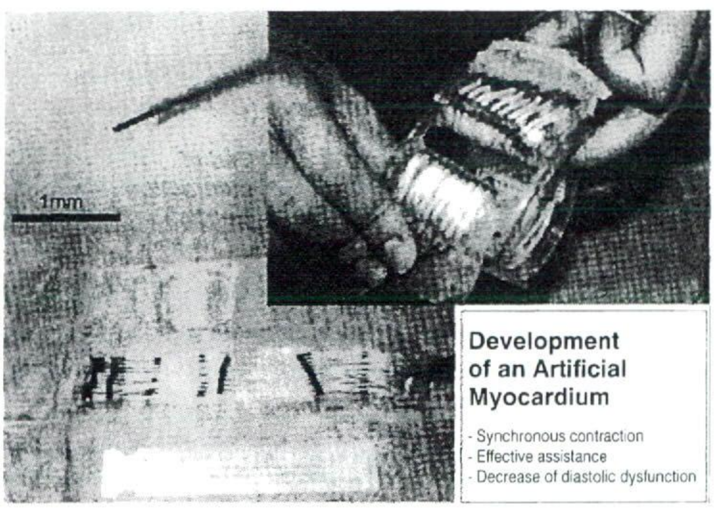

Fig. 4. A shape memory alloy fibre covered by a silicone tubing (upper left), and a prototype of artificial myocardium developed in this study (bottom left); the artificial myocardial fibres were covered with waterproof polymers

(2) Animal experiments

Prior to the measurement, the myocardial assist device was installed in the thoracic cavity and anchored onto the surface girdling the heart by under general anesthetising procedure. The hemodynamic waveforms were obtained from healthy goats, the mean weight of which was 53 kg. Pulmonary and aortic blood pressures were measured by transducers and amplified with a polygraph (Fukuda Denshi, MCS-5000). The aortic flow rate was also measured at the aortic root by an ultrasonic flowmeter (Transonic Systems, TS420). Each data was digitally recorded with a data recorder (TEAC, LX-10) by the sampling frequency of 1.5 kHz.

All the animal experiments related to this study were scrutinised and approved by the Ethical Committee on Animal Experiments of the Department of Medicine, Tohoku University, and also the Institute of Development, Aging and Cancer, Tohoku University, 2004–2006.

3. Results and Discussion

Figure 5 shows the transient response of the Biometal fibre under the different input conditions. The duty ratio was changed from 50 to 300msec, and there was no discernible variation of the speed of the stress gain. As the actuation was conducted only by the cooling-and-heating process in the fibre, neither a sound nor an electric noise could be easily generated in each part.

The myocardial device developed was successfully installed into the goats' thoracic cavity. Prior to the installation of the device, it was covered with silicone rubber

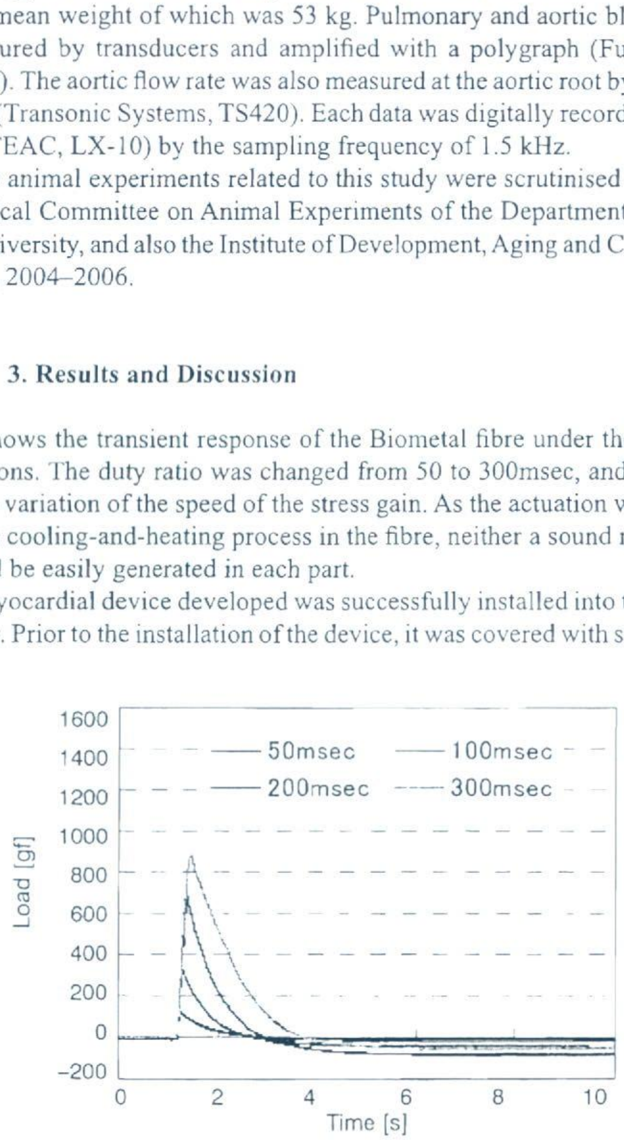

Fig. 5. Basic characteristics of the transient response obtained from a single fibred module under the different pulse wave modulation input conditions; the duty of the input was set to be 50, 100, 200, 300 msec respectively at the room temperature (25°C)

and PVC polymer. For the installation of the former electrohydraulic myocardial assist device, which was developed by the authors [6], it was necessary to remove at least the fifth costa to make enough room to fit it into the thoracic cavity. But in this study, by using shape memory fibres, the actuator itself was so small that it would require even a smaller volume in the thoracic cavity. Moreover, the procedure of the closed chest was found to be much simpler. However, any other complications which might have been associated with the operation were not confirmed in goats yet.

Hemodynamic waveforms were changed by the mechanical assistance as shown in Fig. 6. 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 2.5 l/min by the mechanical assistance. Therefore, it was indicative of the point that the effective assistance might have been achieved by using those shape-memory alloy fibres.

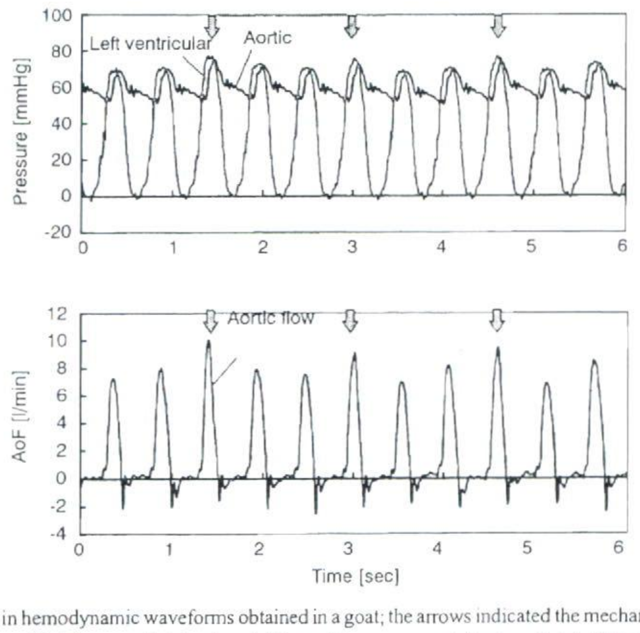

Fig. 6. Changes in hemodynamic waveforms obtained in a goat; the arrows indicated the mechanical contractile assistance by the artificial myocardial developed. The assistance was carried out one third of the natural heart beat

4. Conclusion

The newly-designed mechano-electric artificial myo-cardium was developed by using a shape memory alloy fibre, which was capable to be totally installed into the thoracic cavity. It was easy to attach the device onto the ventricular wall. And also the preliminary examination of the performance of the device was conducted in goat experiments. The amelioration of the cardiac functions following the changes in the vascular hemodynamics were investigated by the mechanical assist. As our system could be a symbiotic autonomous system which is capable of assisting natural ventricular functions with physiological deficit, it might be useful for the application in patients with chronic heart failure, such as angina of effort, and also as the cardiac massage in life-saving emergency for the recovery from ventricular fibrillation, as an alternative circulatory support.

Acknowledgments

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Mechanical integrative design for sophisticated artificial myocardial contraction

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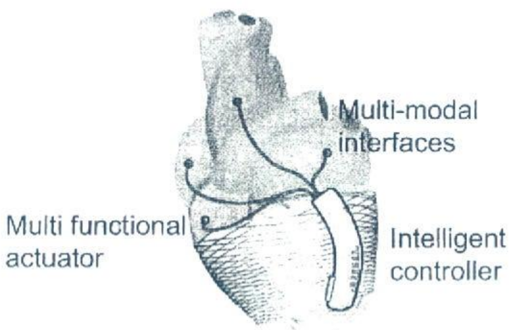
Abstract

The authors have been developing an artificial myocardium by using a covalent-type shape memory alloy fibre, which is capable of supporting ventricular contractile function in each severe heart failure patient. In order to improve its effective assistance from outside of the heart, the anatomical myocardial structure in a goat's heart had been scanned by CT, and the oblique design of the artificial myocardial assist device was reproduced which was to represent native cardiac construction. And the cardiac wall-thickening effect was mechanically simulated by using hinge structures which were connected sequentially. Basic characteristics and hemodynamic effects of the circumferential or oblique types were examined in goat experiments (n=4) as well as in the mock circulatory system. The results were as follows: a) In the hydrodynamic test using the mock circulatory system, the volume assisted which was elevated by 39% by morphological design, b) Hemodynamic data obtained in goats indicated the more effective volumetric assistance by the oblique design. Therefore, it was suggested that the morphological design of artificial myocardial support system could be more effective for the functional improvement of artificial myocardium as well as its control system design.



Contraction by Joule heating: *highly effective actuator*
Strong contractile force: *around 10N/unit (D=150um)*
High durability: *> 900 million cycles (still on going)*
Contractile frequency: *1-3 Hz*
Electrical resistance: *linear against the % shortening*

Fig. 1. Schematic illustration of a concept for the sophisticated mechanical contractile assistance by using the artificial myocardium with shape memory alloy fibre (upper), and the special features of the covalent structured shape memory alloy material (bottom).

1. Introduction

In general, patients with the end stage of severe heart failure, who present an increased ventricular filling pressure or insufficient amount of blood supply to organs, are given medical or surgical treatment. Recently, artificial circulatory assistance by using ventricular assist devices, such as artificial hearts, has been provided, which is followed by heart transplantation. However, the deficiency of donor hearts might be a serious problem in the world. And the transplantation waiting period in this country extends to several years [1]. Therefore, necessity of clinical application of artificial hearts with long-term durability has arisen. As the size of the western ventricular assist devices, which are provided at present, is still big for the smaller body size Asian people, several artificial heart projects are being conducted in Japan, and one of these has started clinical trials.

There are also some devices or procedures suggested to be useful for the surgical treatment of severe heart failure, such as the ventricular CorCup or Myosplint. However, those procedure for the surgical treatment might not provide the active contractile assistance for diseased heart although the diastolic dilatation could be chronically and statically prevented [2-5].

As the heart failure is caused by a lessening of myocardial contractile tension, the direct mechanical myocardial assistance in response to physiological deficit, i.e. a synchronous support of the contractile function from outside of the heart, might be effective. The purpose of this study was to develop an artificial myocardium, which would be capable of supporting the cardiac contraction directly by using the shape memory alloy fibre of a minute diameter around 100um based on nanotechnology.

The authors have been developing a totally-implantable artificial myocardial assist device [6-10]. In this study, the authors fabricated a newly-designed oblique structure and wall-thickening components for contraction by using our shape memory alloy fibred myocardial assist device, and examined thier hydrodynamic or hemodynamic functions in the originally-designed mock circulatory system as well as in goats.

2. Methods

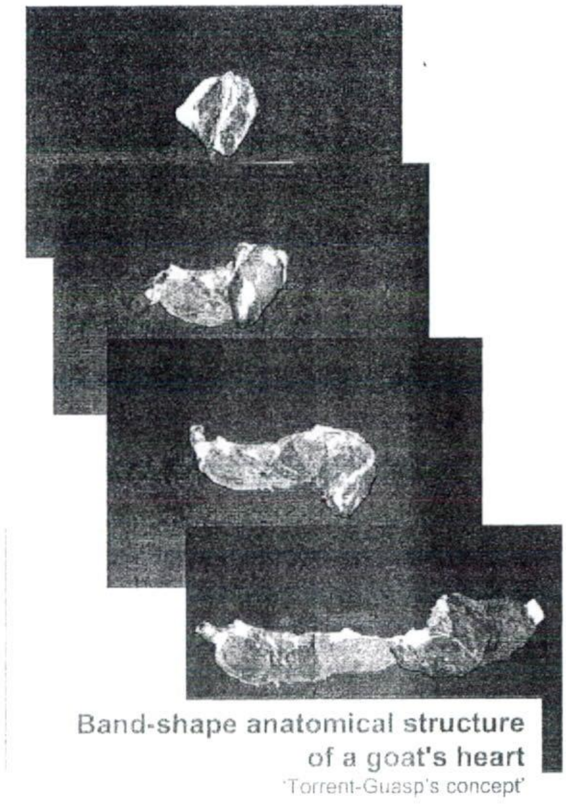
2.1. Anatomical structures of the heart

In order to investigate the native anatomical myocardial structure, a goat' heart was unfolded in accordance with Torrent-Guasp's theory [11,12] as shown in Figure 2. Myocardial streamlines from the apex to aortic root could be investigated by the removal of the right ventricular wall, and its angle against the longitudinal axis of the left ventricle seemed to be around 40-45 degree.

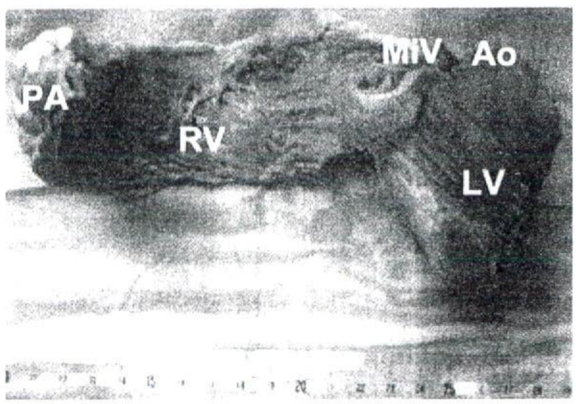
And also the three-dimensional figure had been reconstructed by the computed tomography (Siemens, Somato Definition) as shown in Figure 3. Then inner layered structure and myocardial streamlines of the heart could be investigated.

2.2. Angular and oblique design of the myocardial assist device

Based on the measurement of anatomical structure of the heart, an angular and an oblique shape types of myocardial assist device, which would be able to girdle the ventricle along with the myocardial streamlines, were fabricated as shown in Figure 4. In the angular type, two components of the shape memory alloy band were connected, and the direction of each component was set to be parallel with myocardial streamlines. And in the oblique type, the band was straight shaped along with the parallel-linked shape memory alloy fibres.



(a) Sequential representation of the myocardial structure unfolded of a goat heart.



(b) An unfolded portion of the left ventricle treated by formalin-fixation; myocardial tissue streamline for the morphologic spatial configuration could be investigated at the 'LV' portion

Fig. 2. Band -shape anatomical structure of a goat heart unfolded according to Torrent-Guasp's anatomical concept.

2.3. Built-in 'solid' truss implementation in the device

For more sophisticated representation of native cardiac contraction as shown in Figure 5, as well as the effective magnification of contractile volumetric assistance, a built-in truss mechanism had been implemented on the artificial myocardial band (Figure 6). And its performance was also examined in the mock circulatory system simulating the normal systemic circulatory afterload.

3. Results and Discussion

3.1. Hydrodynamic and hemodynamic effects of different types of myocardial assist device

The oblique design of the myocardial assist device was made to form the contractile streamlines from the apex to ascending aorta. Basic characteristics and hemodynamic effects of the circumferential or oblique types were examined in goat experiments (n=4) as well as in the mock circulatory system. The results were as follows:

a) In the hydrodynamic test using the mock circulatory system, the volume assisted which was elevated by 39% by morphological design.

b) Hemodynamic data obtained in goats indicated the more effective volumetric assistance by the oblique design, and on the other hand there was no significant difference in systolic assisted pressure.

Therefore, it was suggested that the morphological design of artificial myocardial support system could be more effective for the functional improvement of artificial myocardium as well as its control system design.

3.2. Hydrodynamic changes by built-in hinge mechanism

In the hydrodynamic test, the aortic forwarded flow rate was increased by 20% (from 2.8 to 3.4 L/min) against 75mmHg afterload by the 'solid' hinge mechanism implemented. And the ventricular pressure which was measured in the silicone left ventricular model was also elevated by 12%.

4. Conclusion

The mechano-electric myocardium was developed and improved by mechanical integrated design by using shape memory alloy fibres. The device was able to be totally installed into the goat's thoracic cavity. The amelioration of the cardiac functions following the changes in the vascular hemodynamics were investigated by the mechanical assist. As our system could be a symbiotic autonomous system which is capable of assisting natural ventricular functions with physiological deficit, it might be useful for the

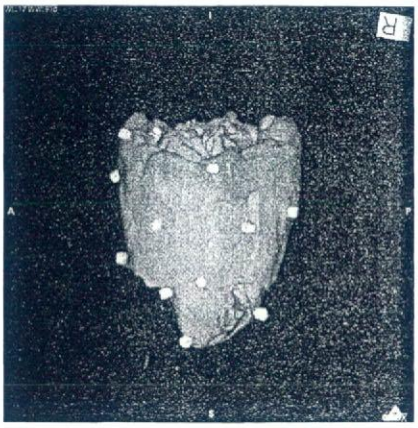
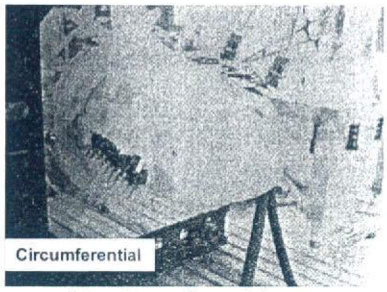
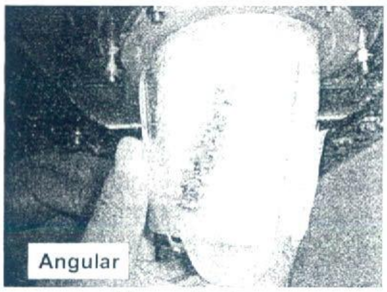


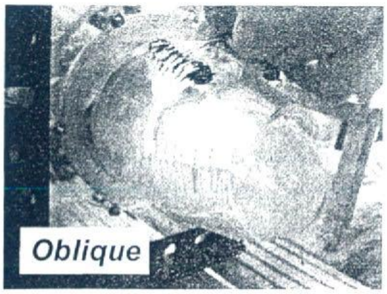
Fig. 3. Numerical reconstruction of the goat's heart from the data measured by MDCT; the white-coloured plastic markers indicated the centre and the edges at each portion of myocardial band unfolded.



(a) circumferential-type



(b) angular-type



(c) oblique-type

Fig. 4. Three different types of prototype models for the artificial myocardial support, which were attached on the silicone left ventricular model.

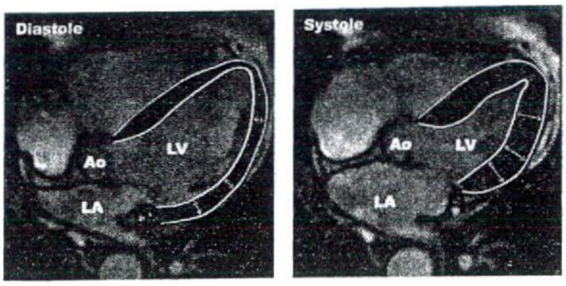


Fig. 5. Normal cardiac contraction and wall-thickening effect obtained at a healthy subject by MRI.

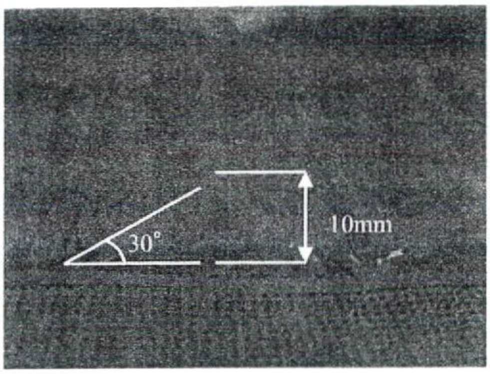


Fig. 6. Newly-designed built-in 'solid' hinge implemented in the myocardial assist device.

application in patients with chronic heart failure such as angina of effort, and also as the cardiac massage in life-saving emergency for the recovery from ventricular fibrillation, as an alternative circulatory support. And its flexible and self-contractile functions might be also useful for the cardiac functional support as well as the treatment of severe ischemic heart failure, such as ventricular aneurysm, which is primarily treated by surgical ventricular restoration.

All the animal experiments related to this study were investigated and approved by the Ethical Committee on Animal Experiments of Graduate School of Medicine, Tohoku University, and also of the Institute of Development, Aging and Cancer, Tohoku University, 2004-2007.

Acknowledgements

The authors would like to extend their appreciation to Mr. K. Kikuchi and Mr. T. Kumagai for their cooperation in the animal experiments. This study was supported by Grand in Aid for Scientific Research of Ministry of Health, Labour and Welfare (H17-nano-009), and Ministry of Education, Culture, Sports, Science and Technology (17790938, 19689029).

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DOI: 10.2353/ajpath.2007.061191

Cardiovascular, Pulmonary and Renal Pathology

Macrophage Colony-Stimulating Factor Improves Cardiac Function after Ischemic Injury by Inducing Vascular Endothelial Growth Factor Production and Survival of Cardiomyocytes

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Macrophage colony-stimulating factor (M-CSF), known as a hematopoietic growth factor, induces vascular endothelial growth factor (VEGF) production from skeletal muscles. However, the effects of M-CSF on cardiomyocytes have not been reported. Here, we show M-CSF increases VEGF production from cardiomyocytes, protects cardiomyocytes and myotubes from cell death, and improves cardiac function after ischemic injury. In mice, M-CSF increased VEGF production in hearts and in freshly isolated cardiomyocytes, which showed M-CSF receptor expression. In rat cell line H9c2 cardiomyocytes and myotubes, M-CSF induced VEGF production via the Akt signaling pathway, and M-CSF pretreatment protected these cells from H_2O_2-induced cell death. M-CSF activated Akt and extracellular signal-regulated kinase signaling pathways and up-regulated downstream anti-apoptotic Bcl-xL expression in these cells. Using goats as a large animal model of myocardial infarction, we found that M-CSF treatment after the onset of myocardial infarction by permanent coronary artery ligation promoted angiogenesis in ischemic hearts but did not reduce the infarct area. M-CSF pretreatment of the goat myocardial infarction model by coronary artery occlusion-reperfusion improved cardiac function, as assessed by hemodynamic parameters and echocardiography. These results suggest M-CSF might be a novel therapeutic agent for ischemic heart disease. ***(Am J Pathol 2007, 171:1093–1103; DOI: 10.2353/ajpath.2007.061191)***

The administration of angiogenic growth factors such as vascular endothelial growth factor (VEGF) is an innovative strategy to treat myocardial ischemia. VEGF has been used in animal models and in clinical trials of myocardial ischemia to develop growth of collateral blood vessels and to promote myocardial perfusion, and its therapeutic potential has been reported.[1–3] Hematopoietic growth factors are potent therapeutic agents for myocardial infarction. Erythropoietin improved cardiac function after myocardial infarction.[4,5] Granulocyte colony-stimulating factor (G-CSF) improved cardiac function and prevented cardiac remodeling after myocardial infarction.[6] A combination of stem cell factor and G-CSF treatment improved cardiac function and survival after myocardial infarction.[7] Macrophage colony-stimulating factor (M-CSF) in combination with G-CSF improved ventricular function after myocardial infarction in rats, but few results were shown by M-CSF treatment alone, and their mechanism was not defined.[8] Moreover, to estimate growth factor-induced therapeutic angiogenesis in hearts, large animal models are necessary,[3] but the effects of M-CSF in large animal models have not been reported. M-CSF has been initially characterized as a hematopoietic growth factor, and has been used to prevent severe infections in myelosuppressed patients after cancer chemotherapy.[9,10] M-CSF stimulates the survival, prolifera-

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