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Development and Hydrodynamic Evaluation of a Novel Inflow Cannula in a Mechanical Circulatory Support System for Bridge to Decision

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Abstract: Recent progress in the development of implantable rotary blood pumps realized long-term mechanical circulatory support (MCS) for bridge to transplant, bridge to recovery, or a destination therapy. Meanwhile, a short-term MCS system is becoming necessary for bridge to decision. We developed a novel inflow cannula for the short-term MCS system, which gives sufficient bypass flow with minimal invasion at insertion, and evaluated its hydrodynamic characteristics. The novel inflow cannula, named the Lantern cannula, is made of elastic silicone reinforced with metal wires. The cannula tip has six slits on the side. This cannula tip can be extended to the axial direction by using an introducer and can be reduced in diameter, and the Lantern cannula enables easy insertion into the left ventricle apex with minimal invasion. The sufficient bypass flow rate can be obtained due to low pressure loss. Moreover, this Lantern shape also resists suction complication around the cannula tip. The pressure loss through the Lantern cannula was measured using a mock circulation and compared with two commercially available venous cannulae (Sarns4882, Terumo, Tokyo, Japan and Stockert V122-28, Sorin Group, Tokyo, Japan), which have almost same diameter as the Lantern cannula. Moreover, the flow patterns around the cannula tip were numerically analyzed by computational fluid dynamics (CFD). Acute animal experiment was also performed to confirm the practical effectiveness of the Lantern cannula. The pressure loss of the Lantern cannula was the lowest compared with those of the commercially available venous cannulae in in vitro experiment. CFD analysis results demonstrated that the Lantern cannula has low pressure loss because of wide inflow orifice area and a bell mouth, which were formed via Lantern shape. The highest bypass flow was obtained in the Lantern cannula because of the low pressure loss under pulsatile condition in in vivo experiments. The Lantern cannula demonstrated superior hydrodynamic characteristics as the inflow cannula in terms of pressure loss due to its specially designed Lantern shape. **Key Words:** Inflow cannula—Mechanical circulatory support—Pressure loss—Bridge to decision.

Recent progress in the development of rotary blood pumps as implantable left ventricular assist devices (LVADs) have realized long-term mechanical circulatory support (MCS) as a bridge to transplantation, a bridge to recovery, or a destination therapy (1–5). Meanwhile, bridge to decision use is increasing, in which stabilization of a patient's hemodynamics is attempted by short-term MCS before applying implantable LVADs. The therapeutic strategy of using expensive implantable LVADs selectively to patients whose hemodynamics are stable is important from a viewpoint of medical cost. Hence, the clinical needs for a short-term MCS device that can be applied up to 1 month are growing rapidly as the long-term therapies using an implantable LVADs increase in number (6–8).

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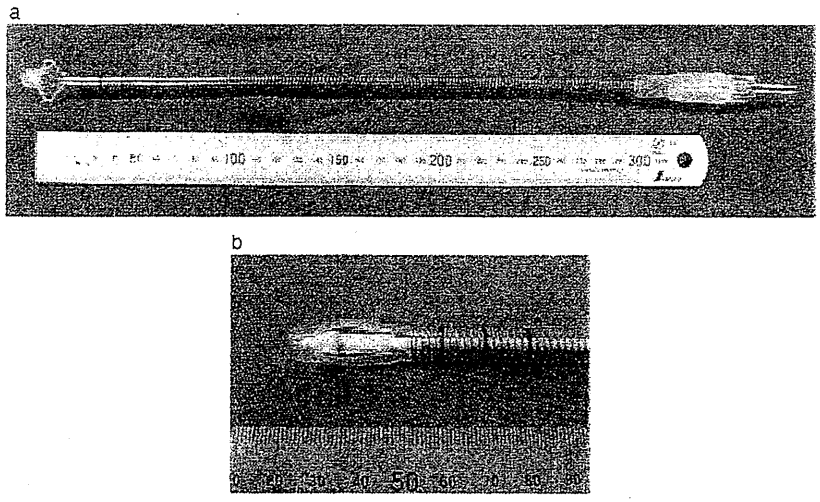

FIG. 1. Picture of the Lantern cannula.

One of the problems in applying a short-term MCS is exacerbation of the cardiac and the physical function via invasion of installing the inflow cannula. The inflow cannula is generally installed into the left ventricle (LV) via the apex on cardiac arrest or ventricular fibrillation with cardiopulmonary bypass (3–5). However, forcing a complex and lengthy operation plus cardiac arrest or cardiopulmonary bypass on a patient with intrinsic cardiac dysfunction can worsen to the patient's heart or multi-organ failure. Therefore, the short-term MCS system requires a small inflow cannula, which enables easy and quick insertion without cardiopulmonary bypass and gives sufficient bypass flow in order to stabilize a patient's hemodynamics and key organ function.

We developed a novel inflow cannula to meet the requirements for the short-term MCS system described above. This cannula was designed to achieve minimal pressure loss and easy insertion at the same time. The present study describes the hydrodynamic characteristics examined using a mock circulation. Computational fluid dynamics (CFD) analysis was also performed to examine its flow patterns. In addition, an acute animal experiment was carried out to assess the efficacy of developed inflow cannula.

MATERIALS AND METHODS

Description of the Lantern cannula

The newly developed inflow cannula, named the Lantern cannula, for the short-term MCS system in left heart bypass is depicted in Fig. 1a. The Lantern cannula is made of elastic silicone and the cannula tip has six slits on the side. The cannula tube is reinforced with metal wires to maintain the shape of cannula against negative pressure or a kinking. The dimensions of the Lantern cannula are given in Table 1.

The features of the Lantern cannula are as follows: (i) This cannula tip can be extended in the axial direction with the introducer so that the diameter reduces at the time of insertion (as shown in Fig. 1b). The Lantern cannula enables easy and quick insertion into the LV apex with minimal invasion without cardiopulmonary bypass; (ii) After the removal of the introducer, the cannula tip immediately returns to the Lantern shape. The inflow orifice is wide open in all directions due to its Lantern shape, and the pressure loss will be relatively low; (iii) This Lantern shape is also expected to prevent suction around the cannula tip. In this article, the suction is defined as the declining of flow rates due to the blockage of the cannula tip by the left ventricular walls.

Measurement of the hydraulic loss

The pressure loss through the Lantern cannula was measured using the mock circulation. The mock circulation consisted of the cannula, a centrifugal pump (Rotaflow, MAQUET Cardiopulmonary AG, Hirrlingen, Germany), two overflow-type reservoirs, a 3/8 in. connector, and a connecting tube, as illustrated in Fig. 2. The cannula tip was installed to the overflow-type reservoir. Tap water (viscosity of 0.001 Pa.) at

TABLE 1. *Size of the Lantern cannula*

Outer diameter (mm)	9
Inner diameter (mm)	7.3
Maximum diameter at slit (mm)	25
Tip hole diameter (mm)	4
Length (mm)	350
Connector size (inch)	3/8

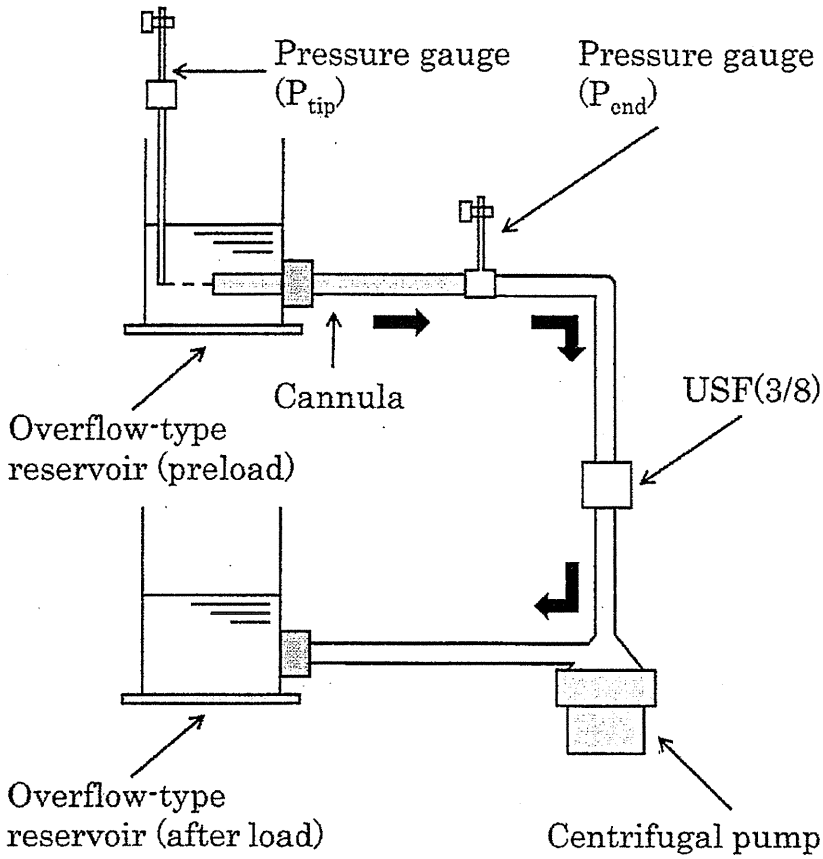

FIG. 2. Schematic diagram of the mock circulation for the evaluation of pressure loss of cannula. USF, ultrasonic flowmeter .

15°C was used as the working fluid in the mock circulation, and the free surfaces of each reservoir were set at 10 and 100 mm Hg. The flow rate was measured using an ultrasonic flowmeter (USF) (T106, Transonic Systems, Ithaca, NY, USA) attached to the tube near the pump inlet. The pressures at the cannula tip (P_{tip}) and at the cannula end (P_{end}) were measured using a pressure gauge (PA-500, Nidec Copal Electronics Corporation, Tokyo, Japan).

The flow rate was regulated at 1 L/min intervals from 1 to 7 L/min by changing the rotational speed of the centrifugal blood pump. The pressure loss through the cannula was calculated from the following equation:

$$\text{Pressure loss} = P_{tip} - P_{end}. \quad (1)$$

The pressure losses of the two commercially available venous cannulae (Sarns4882, Terumo, Tokyo, Japan and Stockert V122-28, Sorin Group, Tokyo, Japan) of almost the same diameter (Fig. 3) were also measured with the same circuit for comparison. The length of these cannulae was adjusted to 350 mm.

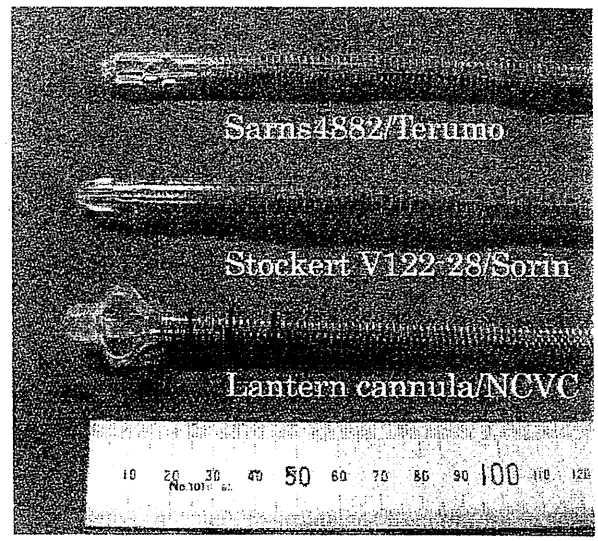

FIG. 3. Picture of three kinds of cannula (Sarns4882 [Terumo], Stockert V122-28 [Sorin Group], and Lantern cannula).

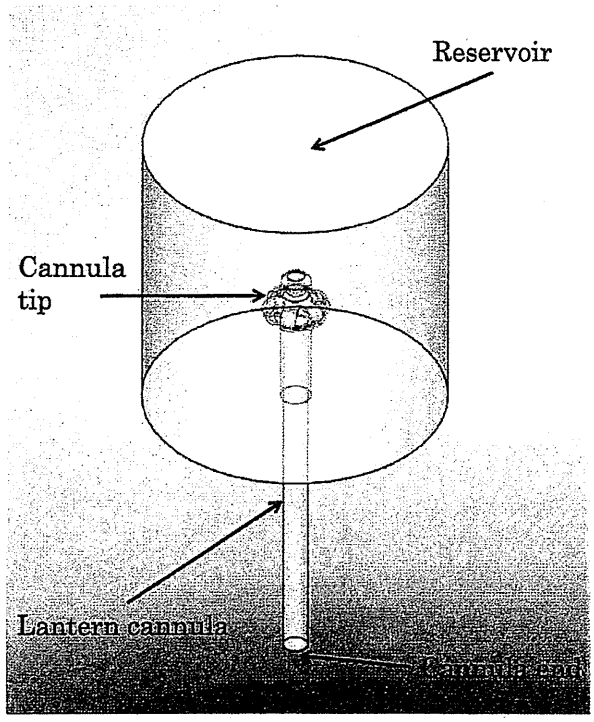

FIG. 4. Analysis model of the Lantern cannula in the CFD analysis.

CFD analysis

CFD analysis was conducted to compare the flow patterns around the tips of the three cannulae. Figure 4 shows an analysis model of the Lantern cannula in CFD analysis. This model was designed using the three-dimensional computer-aided design (CAD) software Solidworks2010 (SolidWorks Japan K.K., Tokyo, Japan). The analysis model focused on the verification of the measured pressure loss in the mock circulation. Therefore, the cannula tip was inserted into a wide reservoir, as well as the mock circulation, and the elasticity of the struts was neglected in the computation of the flows. The numerical cells consisted of the flow path of the cannula and the reservoir. The total number of the numerical cells was approximately 1 000 000. The commercial CFD solver SCRYU/Tetra Ver. 8 (Software Cradle Co., Ltd., Osaka, Japan) was used to solve the velocity and the pressure fields. The working fluid was assumed to be a Newtonian fluid with a viscosity of 0.001 Pa·s and a density of 1050 kg/m^3. The Reynolds number calculated from the diameter and the average flow velocity in the cannula was approximately 1.5×10^4, and the shear stress transport k-ω turbulence model was employed in this analysis. The mass flow rate was regulated at the inlet surface (top of the reservoir), nonslip conditions were set at the walls of the cannula and reservoir, and constant static pressure, 0 Pa, was set at the cannula end. The other two cannulae (Sarns4882, Terumo and Stockert V122-28, Sorin Group) were also analyzed in the same analysis and boundary condition. In terms of the CAD data of the two commercial cannulae, the measured values from each product were used.

Acute animal experiment

An acute animal experiment was performed to assess the hydrodynamic performance in a more realistic setting using an adult goat weighing 51.4 kg. Left heart bypass circuit, which consisted of inflow and outflow cannulae, the 3/8 in. tube, and the centrifugal pump, as well as in vitro experiments, was installed on the beating heart without cardiopulmonary bypass (Fig. 5). The inflow cannula was inserted into the LV apex with a cuff, and the outflow cannula with graft was sutured onto the descending aorta. The bypass flow in the circuit was measured using an USF (T106, Transonic Systems) attached to the pump inlet. The pressures at the distal end of the cannula ($P_{end\_in\ vivo}$) were measured using the polygraph (NEC, Tokyo, Japan). Aortic pressure (AoP), central venous pressure (CVP), and LV pressure (LVP) were monitored with the polygraph with fluid-filled catheters placed in the respective vessels. Rotational speed of the centrifugal blood pump was controlled at 500 rpm intervals from 1500 to 3500 rpm, and the hemodynamics, bypass flow, and $P_{end\_in\ vivo}$ were measured. The pressure loss at the inflow cannula in in vivo experiment was calculated from the following equation:

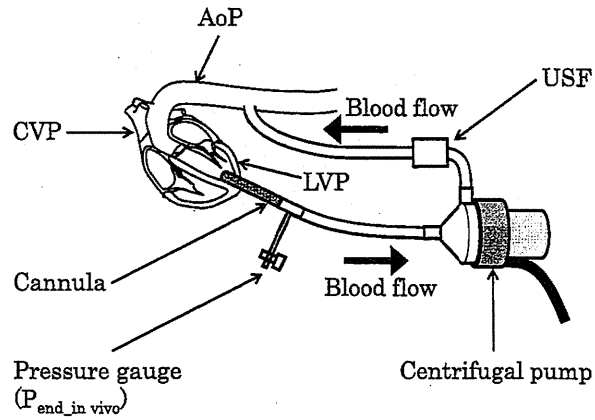

FIG. 5. Schematic drawing of left heart bypass circuit in the acute animal experiment. USF, ultrasonic flow meter.

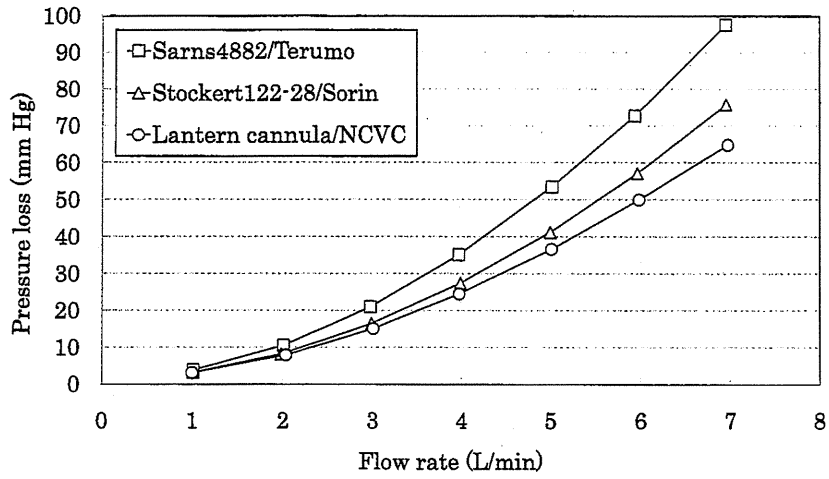

FIG. 6. Pressure loss versus flow rate characteristics in the mock circulation.

$$\text{Pressure loss in in vivo experiment} = LVP - P_{\text{end\_in vivo}}. \quad (2)$$

The pressure losses of Sarns4882 (Terumo) and Stockert V122-28 (Sorin Group) were also measured using the same animal by exchanging only the inflow cannulae during the experiment. Then, the hemodynamics were maintained to realize almost the same conditions in exchange of the cannula.

Institutional guidelines for the care and use of laboratory animals were observed. All protocols were reviewed and approved by the Animal Subjects Committee of the National Cerebral and Cardiovascular Center.

RESULTS

Measurement of the hydraulic loss

Figure 6 shows the results of pressure loss measurement. The pressure losses are plotted against the flow rates. Pressure loss in each cannulae increased nonlinearly with increasing flow rate, and the characteristic approximated to the quadratic curve was obtained. Pressure losses at the flow rate of 5.0 L/min of the Lantern cannula, Stockert V122-28 (Sorin Group), and Sarns4882 (Terumo) were 36.6, 41.2, and 53.6 mm Hg, respectively. The pressure loss of the Lantern cannula seems sufficiently low as an inflow cannula of a left ventricular assist system, and the pressure loss of the Lantern cannula was lowest of the three cannulae at each flow rate, compared with Stockert V122-28 (Sorin Group) and Sarns4882 (Terumo).

Figure 7 shows the rotational speed versus flow rate characteristics. The rotational speeds at the flow rate of 5.0 L/min of the Lantern cannula, Stockert V122-28 (Sorin Group), and Sarns4882 (Terumo) were 2355, 2385, and 2475 rpm, respectively, and the rotational speed of the centrifugal blood pump at the Lantern cannula was also the lowest.

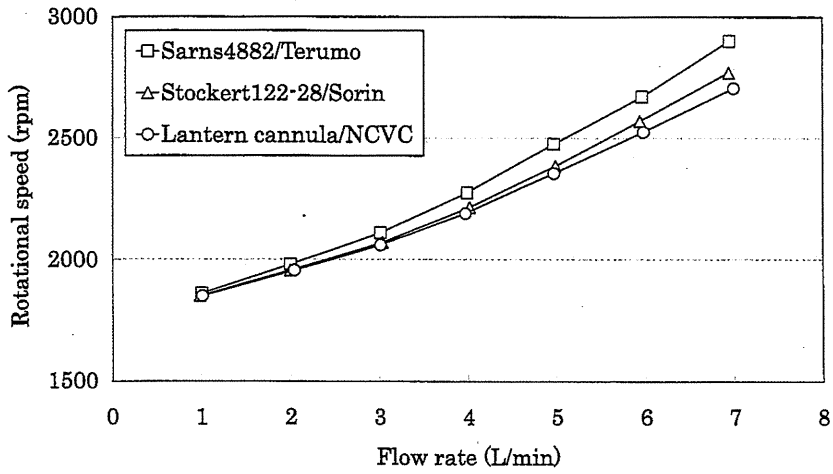

FIG. 7. Rotational speed versus flow rate characteristics in the mock circulation.

TABLE 2. *Calculated pressure loss in the CFD analysis*

Cannula	Calculated pressure loss in CFD analysis (mm Hg)	Pressure loss in the mock circulation (mm Hg)	Error (%)
Sarns4882, Terumo	60.0	53.6	11.9
Stockert V122-28, Sorin Group	34.0	41.2	17.5
Lantern cannula, NCVC	30.0	36.6	18.0

CFD analysis results

Pressure distributions around the tip of cannula were analyzed to examine the flow patterns. Moreover, the average values of the pressure in the tip and an outlet port were computed from the results of pressure distributions, and the pressure loss of each cannula was calculated from its difference pressure.

Table 2 shows the calculated pressure loss at the flow rate of 5.0 L/min in comparison with the measured results. The discrepancies between CFD analysis and in vitro experiments were less than 20%.

Figure 8 shows the pressure distributions of the three cannulae. As a result of the CFD analysis, all cannulae exhibited the decline of pressure at cannula tip, and a constant pressure was maintained from the tip to the outlet. Pressure in the Lantern cannula decreased gradually from the open slits (as shown in Fig. 8a). Meanwhile, pressures at the cannula tip in Sarns and Stockert decreased rapidly after the fluid passed the side holes (as shown in Fig. 8b,c). Therefore, from the tip to the end of the cannulae, a decrease of pressure in the Lantern cannula was low in comparison with other cannulae.

Acute animal experiment results

The Lantern cannula could be quickly installed into the LV via the apex on the beating heart without cardiopulmonary bypass and coring of the LV.

The hemodynamics of the animal during the experiment are summarized in Table 3. An average and standard deviation of hemodynamics were calculated under almost the same experimental conditions with each cannula.

The pressure loss of cannula and the rotational speed versus bypass flow characteristics in the acute animal experiment are shown in Figs. 9 and 10, respectively. Each plot was averaged in 10 s at steady

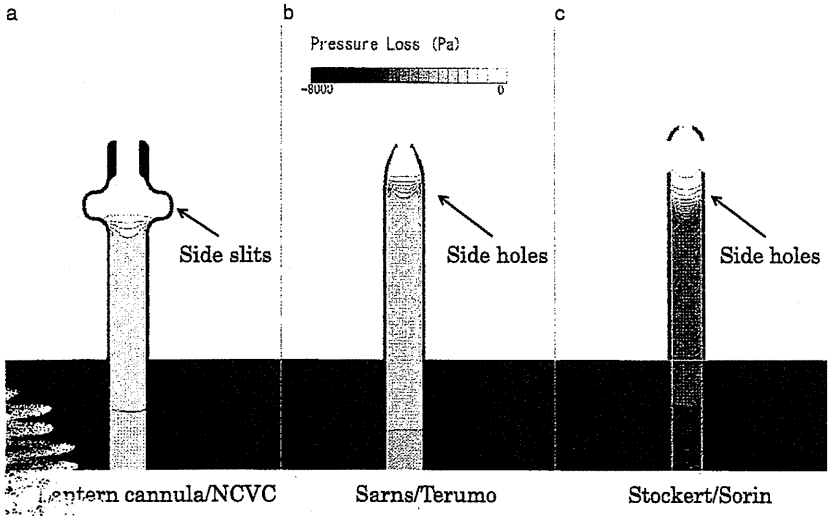

FIG. 8. Pressure distribution of the three cannulae in the CFD analysis.

TABLE 3. *Hemodynamics of goat during in vivo experiment with each cannula*

Cannula	Heart rate (bpm)	AoP (mm Hg)	CVP (mm Hg)
Sarns4882, Terumo	90.8 ± 0.3	94.0 ± 2.0	11.7 ± 0.1
Stockert V122-28, Sorin Group	91.4 ± 0.5	99.6 ± 1.1	11.4 ± 0.1
Lantern cannula, NCVC	96.8 ± 0.4	108.9 ± 4.4	12.8 ± 0.3

bpm, beats per minute.

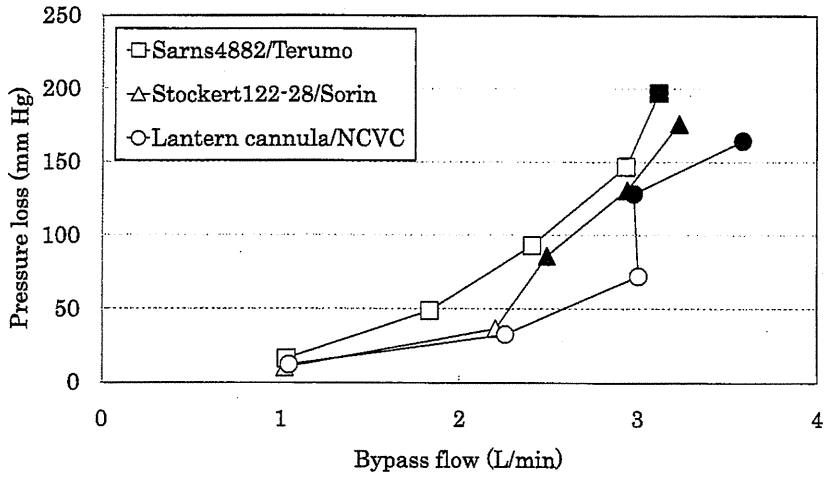

FIG. 9. Pressure loss versus bypass flow characteristics in in vivo experiment.

hemodynamics in these graphs. The pressure loss of the Lantern cannula was lower than the other cannulae at each bypass flow under pulsatile conditions. However, the characteristic approximated to the quadratic curve of each cannula was not obtained, such as in vitro experiments. The maximum bypass flows at rotational speed of 3500 rpm of the Lantern cannula, Stockert V122-28 (Sorin Group), and Sarns4882 (Terumo) were 3.6, 3.2, and 3.1 L/min, respectively, and the highest bypass flow was obtained in the Lantern cannula at the same rotational speed.

DISCUSSION

Recently, there is a growing demand for application of the short-term MCS (6–8), and it is thought that its application will increase further from now on. The short-term MCS system should be easy to install and enable a simple and short operation with minimal invasion because complex and lengthy operations with cardiopulmonary bypass become a burden to the patient. Additionally, it is crucial to obtain sufficient bypass flow to stabilize a patient's hemodynamics. Thus, it is considered that not only a high performance blood pump but also the inflow cannula with low pressure loss is required in a short-term MCS system. Our idea of the Lantern cannula with its unique structure has a potential to meet this need.

In this article, the hydrodynamic characteristics of the Lantern cannula were compared with those of the two commercially available venous cannulae because the dedicated inflow cannula for the LV is not present other than in the LVAD components; however, these two commercially available venous cannulae have a possibility to be used for the short-term MCS. Therefore, these cannulae were selected as the candidates for comparison against the Lantern cannula.

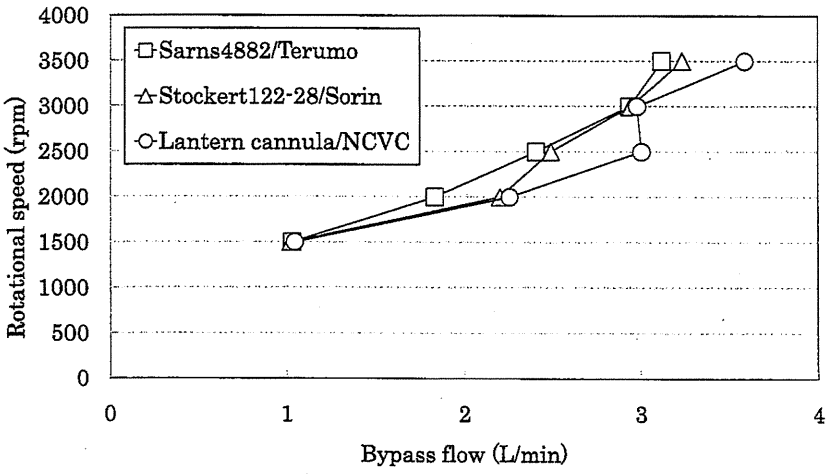

FIG. 10. Rotational speed versus bypass flow characteristics in in vivo experiment.

The purpose of measurement of the hydraulic loss in the mock circulation is to investigate the hydrodynamic characteristics of the Lantern cannula in comparison with these cannulae to demonstrate its superiority in hydrodynamic resistance. Therefore, this time, we used tap water that has stable viscosity as the working fluid in consideration of the ease of experiments. The measured pressure loss in the mock circulation demonstrated that the pressure loss of the Lantern cannula was sufficiently low and lower than those of the two commercially available venous cannulae. It was considered that the pressure at the cannula tip reduced gradually because a wide inflow orifice area and a bell mouth were formed via the Lantern shape. The result indicates that the rotational speed of the blood pump of aspiration via the Lantern cannula is relatively low. This may reduce the risks of hemolysis, thrombus around the bearing due to frictional heat, and wear of the bearing of the blood pump.

CFD analysis was performed to compare the pressure loss of the three cannulae and to verify the effectiveness of the Lantern shape. As the results of comparing the CFD analysis with in vitro experiments, although some quantitative difference was observed, the calculated pressure loss in CFD results had similar tendency to in vitro experiments and the validity of CFD analysis was confirmed. The calculated pressure distribution demonstrated that the side slits and holes in each cannula tip affected the pressure gradient, and the decline of pressure in the Lantern cannula was lower than the other cannulae. The side holes of other cannulae are narrow compared with the side slits of the Lantern cannula. As a flow passage area becomes narrow rapidly, the pressure loss of other cannulae is large. Meanwhile, the flow passage area of the Lantern cannula becomes narrow gradually because of a wide inflow orifice area and the bell mouth, which were formed via the Lantern shape. Therefore, it was considered that the pressure in the Lantern cannula tip reduced gradually.

In order to confirm the practical effectiveness of the Lantern cannula, we performed the acute animal experiment using a goat. Generally, a punch or a circular knife is used to core the LV apex at the insertion of the inflow cannula of the LVAD (3–5). In addition, it is necessary to enforce the cardiopulmonary bypass. The diameter of the Lantern cannula tip can reduce using the introducer at the time of insertion; thereby, the Lantern cannula could be quickly inserted in the LV apex on the beating heart without the coring and cardiopulmonary bypass. It was considered that quick insertion of inflow cannula enables a simple and short operation and is effective in an emergency operation. The acute animal experiment showed that the pressure loss of the Lantern cannula was lower than those of the others under in vivo pulsatile condition of LV. Although the experimental conditions were different, these results agreed qualitatively in terms of pressure loss with in vitro experiments, and it was considered that the validity of in vitro and in vivo experiments was confirmed. In the relationship between pressure loss and bypass flow, it was predicted that the pressure loss characteristics approximated to the quadratic curve were obtained in each cannula, as well as in in vitro experiments. However, there were several clearly detached black plots from the quadratic curve. These black plots showed that the suction occurred in each cannula. As a result, pressure loss of the cannula was increased via the suction and showed a large deviation from the quadratic curve. Thus, it was thought that the characteristics of each cannula were against the suction in in vivo experiment, which were expressed in Fig. 9. This result showed that although Sarns4882 (Terumo) resisted the suction, the bypass flow was low due to high pressure loss. Moreover, it showed that the Stockert V122-28 (Sorin Group) tended to generate suction most easily. In contrast, the highest bypass flow was obtained in the Lantern cannula because of the low pressure loss, although the suction finally occurred. It was considered that the wide inflow orifice in the tip of the Lantern cannula was effective in the LV drainage. However, biocompatibility and durability of the Lantern cannula should be evaluated before the Lantern cannula is evaluated as suitable for the short-term MCS in clinical use. In the future, chronic animal experiments are necessary in order to validate that the Lantern cannula is suitable for MCS.

CONCLUSIONS

We developed the Lantern cannula and evaluated its hydraulic performance in in vitro experiments, CFD analysis, and in vivo experiments. The Lantern cannula demonstrated superior hydrodynamic characteristics as the inflow cannula in terms of pressure loss due to its specially designed Lantern shape.

The newly developed Lantern cannula is expected to become a promising inflow cannula for short-term MCS system.

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Challenges in Research and Development, Productization, and Clinical Application of Advanced Medical Devices in Japan

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Challenges in Research and Development, Productization, and Clinical Application of Advanced Medical Devices in Japan

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Introduction

Although advanced medical devices are currently playing important roles in medical services, there are various hurdles to overcome before such medical devices reach the stage of productization and clinical application. In particular, high-risk therapeutic devices rarely achieve practical application domestically, even if they are developed in Japan. Underlying this phenomenon is the current situation that the environment smoothly linking the research and development venue to the stage of productization and clinical application is not yet sufficiently established.

Characteristics of Medical Devices and International Competitiveness of Japan

Advanced medical devices require concentration and fusion of various technologies including material manufacturing, chemistry, machinery, electronics, information technology and biotechnology; multimodal technologies are used in most cases. From the viewpoints of potency and efficacy, advanced medical devices also have a great variety of actions and functions in physical, chemical and biological terms. As a result, the number of medical device items is about 300,000, overwhelmingly greater than that of drugs (about 17,000).[1] When in practical use, no special techniques are necessary for most drugs, but medical devices require professional expertise and handling, sometimes even a procedure or operation for embedding and removal. In addition, a number of specialist personnel including clinical engineers and radiological technicians are involved in the department in charge at a medical institution, although such specialist personnel are limited. Because of these difficulties, the annual number of registered clinical trials is remarkably smaller for medical devices than for drugs (15–20 trials vs. 110–130 trials).[1]

On the other hand, the balance of trade for Japanese medical devices shows that the annual export account is 475.1 billion yen, whereas the annual import account is 1,075 billion yen, indicating an import surplus of approximately 600 billion yen.[2] Although Japan exports a number of diagnostic devices, most therapeutic devices used in this country are imported; therapeutic devices thus account for most of the import surplus. Japan is importing medical devices mainly from the US (53.5%), followed by European countries such as Ireland and Germany. In the meantime, the ratio of research and development cost to sales volume in medical devices is 12.9% in the US and 6.9% in Europe on average, whereas it is 5.8% in Japan. Thus, it is apparent that greater funding is needed for research and development in countries from which Japan is importing medical devices.[3]

Public Consciousness of "Medical Services" and the Stance of Companies Involved in Research and Development of Medical Devices

Japan has been receiving extremely high appraisals,

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ranking first in the world, in the comprehensive evaluation of health performance by the World Health Organization (WHO).[4] Japan also holds the world record for average life expectancy of women alone and women and men as a whole. In addition, the maternal mortality rate is the lowest globally, and the Japanese perinatal mortality is also in the lowest range. Therefore, Japan is a country where women can conceive and give birth to a baby in maximum safety, from an international perspective. On the other hand, the proportion of national medical expenses to gross domestic product (GDP) in Japan is 8.1%, ranking 25th among 39 counties of the Organization for Economic Co-operation and Development (OECD), and at the bottom among the 7 major industrialized countries (G7).[5] The number of physicians is 2.15 per 1,000 population, which is in the lowest range, ranking 23rd among 31 OECD countries. In Japan, people visit hospitals at a 2-fold higher frequency per capita than in Western countries, and society is facing an unprecedented rate of aging with an aging rate of more than 20%. Under these conditions, the number of physicians is overwhelmingly insufficient, hospitals are over-extended, and healthcare collapse is ongoing. However, there is still a tendency for healthcare bashing in society, and people are still lacking in healthcare cost-consciousness.

The negative national consciousness for overall healthcare casts a shadow on the attitude of companies involved in the development of medical devices. Manufacturers in Japan have high quality, and a number of companies hope to make their own technologies useful in the fields of healthcare and welfare. However, particularly with high-risk therapeutic devices, some companies may eventually withdraw even when development of devices has proceeded to the stage of productization. As reasons for such withdrawal, cited are the issues of product liability and the lack of a formulated law corresponding to the US Biomaterials Access Assurance Act. However, their true intent is to avoid the risk of suffering severe damage from harmful rumors. The attitude of the media and harmful rumors that demonize medical institutions and medical devices even without accurate understanding of the situation represent the greatest concern for companies engaged in manufacturing medical devices. This is also the case for material manufacturers that provide parts and materials, and they consider supplying the field of healthcare to be filled with risks and uncertainty.[6] In addition, when the degree of innovation in state-of-the-art devices is higher, the marketability and profit forecasting are less clear, and it is more difficult to maintain perspectives concerning applications for clinical trials and approval or inclusion in the insurance coverage list. These are major obstacles to companies.

Device Lag

According to the internet survey by the American Medical Devices and Diagnostics Manufacturers' Association (AMDD),[7] 87% of Japanese people consider advanced medical technologies to be important, and 80% want to use the newest advanced technologies available globally, with 66% of them not minding if healthcare costs increase to some extent because of the use of such technologies. On the other hand, there is a device lag in Japan, a so-called time lag vis-à-vis the availability of medical devices, i.e. devices tend to be introduced later in Japan than in Western countries. However, the review period for approval has been shortened in Japan, and there is now no difference in priority review items between Japan and the US. Therefore, it is presumed that the ability to review advanced medical devices in Japan is similar to that in the US, such that the problem would be a deficient quantity of reviews in Japan.[8] The Pharmaceuticals and Medical Devices Agency of the Ministry of Health, Labour and Welfare has formulated an action program to accelerate the process of reviewing medical devices, and aims to shorten the period required for approval of new medical devices by 19 months over five years. Another aspect of device lag in terms of the number of approved medical devices, is that only about half of the types of medical devices available overseas are available in Japan.[1] For about half of such devices not available in Japan, application for approval in this country has not been made because of factors other than procedures for device approval, such as market circumstances and business costs. The commonly long period of time from the end of the review until inclusion in the insurance coverage list is another bottleneck in the medical devices business.

On the other hand, a survey of public attitudes toward medical devices carried out by the National

Cerebral and Cardiovascular Center revealed that more than 90% of people were aware of an increased need for medical devices, and that about 80% wanted an increase in the self-sufficiency rate of medical devices.[9] Thus, it is important to promote the development of advanced medical devices by Japanese companies that have excellent technological foundations, and to facilitate the productization of domestic therapeutic devices in particular, aiming at breaking away from import dependence. These efforts are anticipated to create an environment of clinical application of medical devices free from the issue of device lag.

Various Policies to Promote the Development and Productization of Advanced Medical Devices

The Cabinet Office, the Ministry of Education, Culture, Sports, Science and Technology, the Ministry of Health, Labour and Welfare (MHLW), and the Ministry of Economy, Trade and Industry (METI) formulated the Five-Year Strategy for Creation of Innovative Drugs and Medical Devices in April 2007.[10] This is a set of policies aimed at the promotion of precedent development of medical devices in Japan or the world, i.e. simultaneous development in which Japan is participating, in order to provide Japanese people with drugs and medical devices meeting the highest international standards and to assure that the drug and medical device industry will play the role of leading growth in Japan. On the other hand, the Council on Fiscal and Economic Policy decided to create "super-specific districts" to overcome factors that interfere with the development of innovative technologies, as an action of the Basic Policies 2008 for economic and fiscal reform.[11] As the first district of this type, "the specific district for development of advanced medicine" was started in 2009 to select and support projects of a consortium that is centered on an advanced medicine research base. In addition, as a mainstay project based on the New Growth Strategy issued in 2010 by the Japanese government, medical innovation was given a foundation for strong joint efforts of the public and private sectors to promote medical research and development toward the practical application of new technologies. Through such founding of national strategies defining a significant direction, various problems that had shown no sign of settlement are now gradually being resolved in the areas of research and development and practical application of medical devices.

Support Project for Formulating Guidelines for Development Evaluation of Next-generation Medical Devices

As a specific effort concerning the development of advanced medical devices, we can cite the support project for formulating guidelines for the development evaluation of next-generation medical devices, which was a joint project begun in 2005 by the MHLW and the METI. This project was intended to consider and set up, in advance, evaluation criteria for efficient and rapid investigation and review of various innovative medical devices under development when they enter the stage of non-clinical or clinical trials or the approval process. In the area of artificial organs, the next generation artificial heart as an implantable active device was adopted as a subject of discussion, and guidelines for both development and review of such devices were formulated in 2007 after 2 years of discussion.[12–14] In Japan, two types of domestically produced implantable artificial hearts were approved at the end of 2010, through the process of non-clinical and clinical trials and review and approval according to these guidelines. Thus, in the Japanese system of clinical trials devoid of the mechanism of investigational device exemption (IDE), the burden on companies sponsoring trials evaluating expensive medical devices such as artificial hearts has come to be substantially reduced. Both types of implantable artificial hearts were included in the insurance coverage list in April 2011, and ongoing aggressive clinical application of these devices has saved the lives of many patients.

Conclusion

The healthcare system is part of the basic infrastructure of a nation, and also serves as an important industrial base, including medical devices. Japan has abundant human and technical resources, and is capable of developing world-leading advanced medical devices by concentrating and fully applying its expertise and knowledge. Development of such advanced medical devices, particularly therapeutic devices, confers benefits for many patients not only in Japan but

worldwide. It is desirable that the environment of research and development and clinical application be improved, and that people understand medical services and devices and support their development.

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BRIEF COMMUNICATION

Computational fluid dynamic analysis of the flow field in the newly developed inflow cannula for a bridge-to-decision mechanical circulatory support

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Abstract The flow field of the newly developed inflow cannula designed for a bridge-to-decision circulatory support was numerically analyzed by computational fluid dynamics. This new cannula has elastic struts at the tip that enable minimal invasive insertion into the left ventricle while maintaining a wide inflow area by its lantern-like tip. The cannula's hydrodynamic loss, including change in pressure loss due to deformation, and its thrombus potential were numerically examined. Hydraulic resistance of the cannula with blood analog fluid was 31 mmHg at the flow rate of 5.0 L/min. There were regions on the inner surface of the struts where the shear rate was $<100\ s^{-1}$, and these regions can be a potential for thrombus formation, especially at low flow rates or under limited anticoagulant therapy.

Keywords Cardiogenic shock · Ventricular assist device · Inflow cannula · Thrombus · Computational fluid dynamics

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Introduction

Refractory acute cardiogenic shock is one of the leading causes of death in patients with myocardial infarction, and for many of these patients, mechanical circulatory support (MCS) is the only means of survival [1]. Left-ventricular assist devices (LVADs) have become a reliable therapeutic option for these patients [2]. LVADs have been widely used as a bridge to transplantation (BTT), and the recent progress of implantable systems [3–5] has expanded their application into therapeutic options, including permanent LVAD implantation called destination therapy (DT) for those ineligible for heart transplantation [6]. On the other hand, survival of the patients suffering from multisystem organ failure (MOF) secondary to acute cardiogenic shock remains poor. The only available options for these patients is an LVAD or extracorporeal membrane oxygenation (ECMO), but there are many clinical cases with the situation that installation of an LVAD is not possible due to poor hemodynamics and multiorgan dysfunction. In such cases, a short-term extracorporeal device, the so-called bridge-to-decision (BTD) device, is often applied to maintain and improve hemodynamics and to assess the effectiveness of the LVAD treatment [7]. The design of the inflow cannula, as well as the blood pump itself, is one of the key factors for maximizing the effect of ventricular support with a BTD device. The quick cannulation with a minimum surgical invasion is also required for patients who need urgent treatment. The assisted flow rate is sensitively influenced by the relative position of the cannula tip against the ventricular wall [8], but careful fixation of the inflow cannula is essentially impossible in cases of high emergency. The design of the cannula tip to resist the sucking events, therefore, is highly important [9]. The flow condition inside the inflow cannula is also an important

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design issue. Stasis in the cannula itself can be a potential cause of thrombogenic complications [10] because in patients with bleeding complications, anticoagulant therapies are not an option.

Our research group has been working on developing a superior BTD system, and here we report our findings on the flow field of the novel inflow cannula developed for extracorporeal left-heart bypass [11]. The flow field was computed to estimate the mechanism of hydraulic losses and the stasis potential on the surfaces for future improvement of antithrombogenicity of this cannula.

Materials and methods

Lantern Cannula

The newly developed Lantern Cannula is a silicon inflow cannula for drainage via the apex of the left ventricle. The outer and inner diameters of the tubing are 9 and 7 mm, respectively, and total cannula length is 350 mm. The end of the cannula is fit to a 3/8-in. connector. There are six elasticized struts 10 mm from the top that maintain its expanded position without external forces, as depicted in Fig. 1a.

During insertion, these elastic struts can be deformed in the axial direction with the help of a stylet so that the outer diameter at the struts decreases to approximately 9 mm, which is the same as that of the wire-reinforced tubing (Fig. 1b). The straight part at the top of the cannula, reinforced with the thick tubing wall, is required to resist axial force on the cannula during insertion. After cannula insertion and stylet removal, the cannula recovers its expanded shape in the left ventricle to prevent the inlet portion from total obstruction or from sucking events caused by hypovolemia or poor positioning of the cannula tip.

Computational model

Figure 1c shows the typical computational grid for the Lantern Cannula. The unstructured numeric grid was generated from surface data of the cannula. The configuration of left ventricle, the relative position of the cannula to the left-ventricular wall, and the inserted distance of the cannula all affect flow conditions of the cannula, but simulating all of these parameters that totally depend on the patients' profiles is not considered to be practical. This analysis focused on the effect of configuration of the cannula tip on hydraulic loss and stasis in the cannula with a view to design improvement; therefore, configuration of the left-ventricular walls as the boundary surface was not taken into consideration.

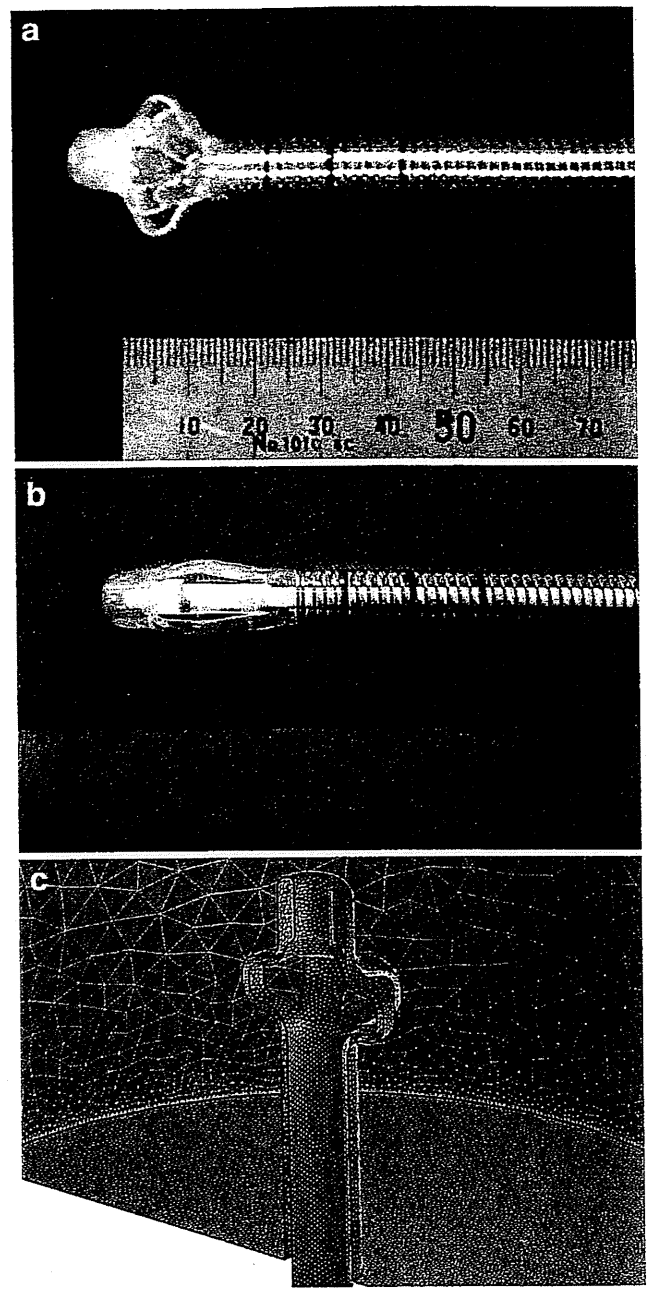

Fig. 1 Configuration of the Lantern Cannula. **a** Expanded tip. **b** Elongated tip with the stylet. **c** Computational grid

A finite-volume-method-based computational fluid dynamics (CFD) package, Scryu/Tetra v.8 (Software Cradle, Japan) was used for numerical computation of fluid velocity and pressure. The blood-analog Newtonian fluid with 1,050 kg/m^3 density and 3.00×10^{-4} Pa/s viscosity was used as the working fluid. The turbulent flow is assumed because the Reynolds number calculated from the diameter and average flow velocity in the cannula was approximately 5.0×10^3. We employed the shear stress transport (SST) k–ω turbulence model in our analysis. The boundary conditions are as follows;

- A constant mass flow rate was given at the inlet part, which is the top surface of the calculated space.
- A constant static pressure, 0 Pa, was set on the outlet surface.
- Nonslip condition was used on the other walls, including those of the Lantern Cannula.

Results

Figure 2a illustrates flow-velocity vectors and pressure contours at the flow rate of 5.0 L/min on the center sections. At the inlet of the tubing portion, a smooth flow is induced without flow separation or reverse flow. The throat of the cannula forms a bell-shaped mouth with the elasticized struts, and this configuration probably contributes to the smooth flow at the inlet. On the other hand, there is flow separation and reverse flow right down the top hole. This area can be a potential for stasis. A large portion of the flow enters from the side slits between the struts, an the flow rate passing through the hole at the tip was 0.38 L/min, 7.7% of total flow rate. Pressure loss at the flow rate of 5 L/min was 4,180 Pa (31.4 mmHg). Pressure decreases rapidly at the throat of the cannula after passing the open area between the struts and steadily along the tubing part. The calculated shear stress contour on the inner surfaces of the cannula is shown in Fig. 2b. The regions where the shear rate is $<250\ s^{-1}$ are considered as the potential of thrombus formation according to the previous study [13], and in Fig. 2c, the stasis potential regions are concentrated between the inlet hole and the struts. The lowest shear rate on the inner surface of the cannula was measured as $45\ s^{-1}$ and was located right down the inlet hole (A in Fig. 2c).

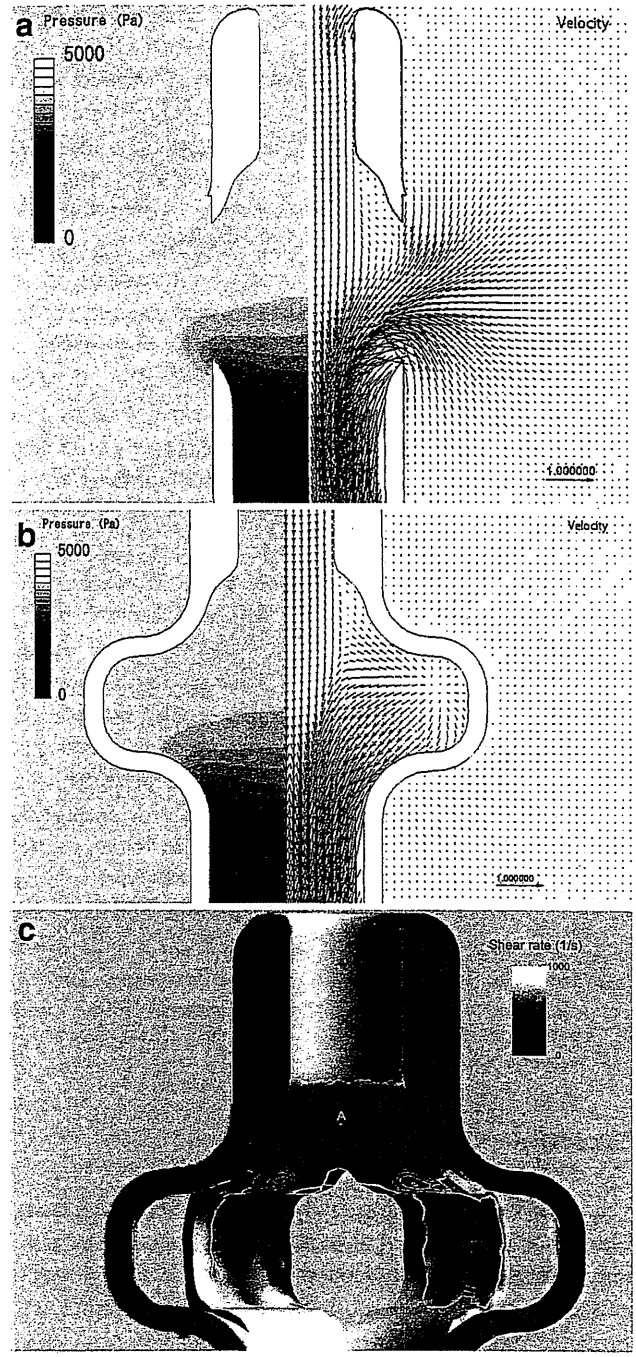

Fig. 2 Computated flow field in the Lantern Cannula. **a** Pressure distribution (*left*) and flow velocity vectors on the central section. **b** Pressure distribution (*left*) and flow velocity vectors on the central section [perpendicular to the section shown in (**a**)]. **c** Distribution of shear rate on the inner surface

Discussion

The Lantern Cannula was developed as an inflow cannula for the left LVAD for BTD use. The unique characteristics of the flexible struts are expected to contribute to less-invasive insertion into the left ventricle and to minimize the hydraulic resistance of the cannula, which was assessed as 31 mmHg at the flow rate of 5.0 L/min with the working fluid of blood analog. This pressure loss is considered to be sufficiently small for an inflow cannula of the LVAD when compared with the other venous cannulae that are used for the same purpose [11]. The six elasticized struts were designed to maintain wide-open side windows, and numeric analysis of the flow field revealed that this configuration is also advantageous to maximize the incoming flow rate due to its bell-shaped mouth at the inlet of the straight tubing part. The inserted distance from the apex can be adjusted from 20 mm to maximize the assisted flow rate. The flow entering the tubing part of the cannula did not seem to cause any separation at the throat. The portion of fluids passing through the tip hole of the cannula, on the other hand, is small, less than 8% of the total flow. This indicates that the dimension of the tip hole is not an influential design factor in terms of

hydraulic resistance of the cannula. This cannula is designed for short-term use, up to 1 month, especially for BTD cases. A BTD use of the MCS system is generally applied with a view to stabilize patients with seriously damaged circulatory status and to evaluate the efficacy of a switch to a long-term support system, such as an implantable LVAD. Anticoagulant and antiplatelet therapies are often limited due to bleeding complication; therefore, the antithrombogenicity of the support system is very important. Antithrombogenicity of the inflow cannula is crucial because once inserted into the left ventricle, the cannula is essentially impossible to exchange. We also used numeric analysis to assess the flow field in terms of thrombus potential. Distribution of wall shear stresses on the blood-contacting surfaces of the Lantern Cannula revealed a region with poor washout on the inner surfaces of the upper part of the struts, as depicted in Fig. 2c. The region where the shear rate is $<250\ s^{-1}$ is reported to be a potential for thrombus formation in the pneumatically driven LVAD [12, 13], and the area of this potential region increases as the flow rate decreases. In real application, however, these poor washout regions will be reduced, if not removed, under the presence of the pulsatile flow by the native heart. The incoming flow rate varies periodically, and the consequent vortices and turbulence will oscillate the flows in these poor washout regions. In addition, the flow entering the cannula is largely subject to the position of the cannula tip inside the left ventricle. We did not consider the configuration of the ventricle as the boundary surface in this study, however, as our intent was to only assess hydrodynamic losses with the newly developed Lantern Cannula. The design consideration toward better antithrombogenicity will be the next issue of development.

Conclusion

Numerical analysis of flow in the newly developed Lantern Cannula was performed. The cannula's unique configuration composed of elasticized struts and side slits, contributed to the small hydraulic resistance of the cannula. The computed flow field revealed the existence of the low-shear-rate region on the inner surface of the cannula, which should be considered in the discussion of anticoagulant therapy for patients with LVAD using this cannula.

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解　説

次世代型人工心臓の開発と臨床応用

巽　　英介

人工心臓は，自然心臓のポンプ機能を代行して全身の血液循環を維持する装置であり，重症心不全患者に対する一時的使用や心臓移植までのつなぎとして広く臨床応用されている．また近年では，半永久的な使用を目的とした体内埋込み型人工心臓の開発・臨床応用も進められており，技術開発の進歩とともに臨床成績も急速に向上しつつある．このような次世代型の人工心臓システムは，心臓移植を受けることができない多くの重症心不全患者を救命するとともに，安全な長期間使用と高い生活の質を提供して社会復帰を実現し得るものであり，日常医療の一環となって多くの患者に福音をもたらす日が1日も早く訪れることが望まれる．

Keywords : artificial heart, ventricular assist device (VAD), total artificial heart (TAH), heart failure, heart transplantation, destination therapy (DT), bridge to transplantation (BTT), centrifugal pump, axial flow pump, quality of life (QOL)

1. まえがき

心臓の最も重要な機能は，全身に血液を送り出すポンプとしての機能であるが，人工心臓はそのポンプ機能を肩代わりする装置である．人工心臓は，1958年にAkutsuらによって初めて動物実験での生存（1.5時間）が報告され[1]，以後開発・改良が進められてきた．1960年代中盤には空気駆動方式の補助人工心臓（Ventricular Assist Device : VAD）の臨床応用が行われて離脱成功及び長期生存例が得られ[2]，1969年及び1981年には空気駆動方式の全置換型人工心臓（Total artificial Heart : TAH）が心臓移植までの一時使用（ブリッジ）として臨床応用された[3]．その後も米国や我が国を中心に継続的な開発が進められ，今日では重症心不全患者に対する一時的使用や心臓移植へのブリッジとして広く臨床応用されるに至っている．しかしながら，人工心臓のブリッジ使用の出口となる心臓移植の症例数には限界があることから，近年重症心疾患患者に対する半永久的な使用を目的とした次世代型の人工心臓開発に対する期待が急速に高まっている．次世代型人工心臓は，安全な長期間使用に加えてある程度の自由な活動を保証し，高い生活の質（Quality of Life : QOL）を患者に提供し社会復帰を実現し得る体内埋込み型のシステムである．本稿では，このような次世代型人工心臓について，最新の研究開発と臨床応用の状況を含めて概説する．

2. 次世代型人工心臓研究開発の背景

心疾患は先進諸国における主要な死亡原因の一つであり，先進国全体で2300万人以上の人々が心不全を患っている．心不全の診断を受けた患者の心原性突然死の頻度は通常の6〜9倍に達し，診断後1年以内に20%，5年以内に50%以上が死亡する．重症心不全患者のQOLは極めて不良で，その症状のために低いQOLの生活を強いられている患者の数は死亡者数の約30倍に達する．米国心臓協会（American Heart Association : AHA）の「Heart Disease and Stroke Statistics」によると，現在米国には1320万人の冠疾患患者（狭心症や心筋梗塞）及び500万人の鬱血性心不全患者が存在するとされ，冠疾患患者による年間死亡数は65万人，また鬱血性心不全患者による年間死亡数は29万人に達する．我が国でも心疾患患者の年間死亡数は約16万人で死因の第2位を占め，臓器別の死因としてはトップキラーである．近年種々の心疾患治療法の発達に伴って多くの患者が救命されるようになりつつあるが，その一方で心疾患罹患数は増加の一途をたどっており，心疾患を克服するための対策の確立は先進諸国における重要な医療政策課題となっている．

現在，不可逆性重症心疾患患者に対する唯一の治療法は心臓移植であるが，ドナーの慢性的かつ圧倒的不足がその症例数を制限しており，心臓移植で救命される患者数は不可逆性重症心疾患患者の僅か数%に過ぎない[4]．我が国においても1997年11月に臓器移植法が発効し心臓移植が再開されたが，現在まで13年間の症例数は僅か73例にとどまっており，かかる重症患者を救命するためには新たな治療方法の開発が必須な状況にある．近年，再生医療に関する研究の進展に伴い，かかる手法の心不全治療への応用が新たな治療手段として期待されつつある．しかしながら，心臓に関する再生医療的治療法の進展と臨床応用の普及に

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は今後さらに相当の期間を要すると考えられ，また重症心不全患者死亡例の多くを占める急性症例においては再生医療的治療では迅速な循環補助効果が得られず，さらに心機能回復効果そのものにも一定の限界が存在すると考えられる．豚心などを利用した異種心臓移植の研究も進められつつあるが，免疫学的問題や未知のウィルス感染の危険性，倫理上の問題などの多くのハードルが存在する．

以上のような状況により，現時点では世界的に，心臓移植までのつなぎとしての人工心臓治療（Bridge to Transplantation：BTT）ないし恒久使用を目的とした人工心臓治療（Destination Therapy：DT）が重症心不全における心臓移植治療を補完または代替する手段として最も有力な選択肢と考えられている．人工心臓をBTT及びDTとして用いるために必要な耐久性としては，それぞれ6カ月及び2年間の「イベントフリー」での使用が目安とされてきたが，後述のようにドナーが少ない我が国ではBTTとしての使用期間が平均で2年を超える状況となっており，実質的にDTに求められる耐久性が必要となる．また，DTの期間も延びつつあり，次世代システムの耐久性の目標は5年間程度は必要となるだろうと考えられる．

米国では，人工心臓の必要性を客観的に評価するために，National Heart, Lung, and Blood Institute（NHLBI）が1989年に各分野の専門家による独立した評価機関Institute of Medicine（IOM）を設立し，多角的な必要性評価を行い，1991年に報告を行っている[4]．それによると，全米において55歳以下で年間1万～1万5000人，75歳以下で年間3万～3万5000人，全年齢で年間6万～7万人の患者が，心臓移植または人工心臓の恒久的使用の絶対的適用対象になり得るという．我が国では人工心臓必要患者に関する同様の推計調査は行われていないが，IOMのデータに基づいて我が国の状況を推察すると，心疾患死亡数を米国の20～25％と仮定した場合，心臓移植または人工心臓の恒久的使用の絶対適応対象となり得る患者数は55歳以下に限っても2000～4000人程度は存在するものと考えられる[5]．

3. 人工心臓の分類

人工心臓は，自己心臓を体内に残したままポンプ機能の一部を代行するVADと，自己心臓を切除してこれと置換して埋め込まれるTAHの二つに大別される．VADは送脱血管によって生体と結合され，血液ポンプは体表または体内に置かれる．左心補助の場合，脱血管は左心室心尖（せん）に，送血管は大動脈に挿入留置または縫着されるのが一般的である．自己心臓のポンプ機能の一部を肩代わりし，全身循環を保って不全心の負荷を軽減するとともに，冠状動脈血流を維持して不全心の回復を促進する．自己心機能が回復すれば離脱し得るが，それが望めない重症例ではBTTあるいはDTとして用いられる．一方，TAHは回復不能となった自己心臓を切除した後に同所性に埋め込まれ，自己心臓のポンプ機能の全てを肩代わりする．VADと比べて

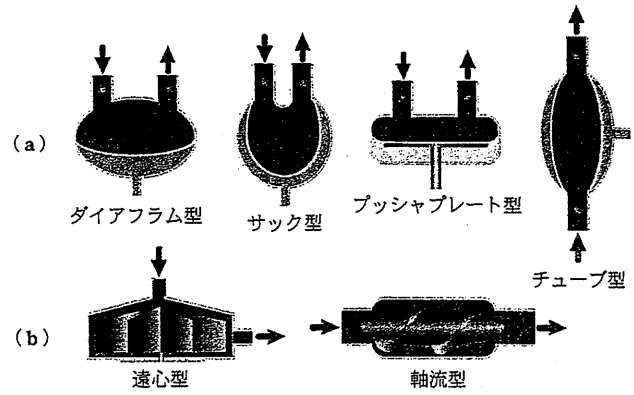

図1　駆出機構からみた人工心臓の分類．拍動流型（a）と連続流型（b）．

より優れた循環維持能力をもつ反面，胸腔内に埋め込まれるために厳格な解剖学的適合性が要求される．自己心臓を切除するため，現状では一部を除いてほぼ全例がBTTとして用いられている．

人工心臓を駆出機構からみた場合には，血液を拍動性に駆出する拍動流型と拍動のない連続流で駆出する連続流型に分類される（図1）．拍動流型は血液ポンプを収縮・拡張させて流入出弁の働きで血液を一方向性に駆出するもので，従来はこのタイプが一般的であった．血液ポンプにはポリウレタンなどの高分子材料が用いられるが，血液と直接接触するために良好な抗血栓性が求められる．駆動源としては圧搾空気による空気圧駆動方式のものが多く用いられてきたが，モータや電磁力を用いた電気駆動方式のものも開発され臨床応用が進められてきた．しかしながら，拍動流型人工心臓は血液ポンプ内の血液量を拍動によって変化させる容積置換型ポンプであるため，どうしてもサイズが大きくなり体内埋め込みが制限されたり拍動に伴う機械的耐久性などが問題となり，近年は主役の座を連続流型人工心臓に譲りつつある．連続流型はモータで羽根車（インペラ）を回転させて血液を送り出す電気駆動方式のターボポンプで，軸流型と遠心型に大別されるが，いずれも血液はポンプ由来の拍動がない連続流の形で駆出される．元来は心臓手術時の体外循環や一時的循環補助を目的に用いられてきたが，構造が単純でエネルギー効率も良好で，また非容積型のため小型化が可能などの利点を有することから，近年では体内埋込み型人工心臓として開発が進められ臨床応用が行われている．さらに，より長期間の使用が可能な連続流システムとして，ベアリング機構を完全になくしてインペラが他の部位と非接触の状態で回転することで耐久性や抗血栓性の向上を図ったシステムも開発されつつある．このような完全非接触型ポンプには，回転するインペラの位置・姿勢を電磁的に能動制御する磁気浮上方式と，ミクロン精度に加工された動圧溝で発生する動圧により受動的制御を行う動圧軸受方式がある．

人工心臓を患者の体にどのように設置するかという観点からは，血液ポンプを体表に置く体外設置型と体内に留置