Research and development of a monopivot centrifugal blood pump for clinical use

— Collaboration for a product between medical and engineering teams —

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[Translation from *Synthesiology*, Vol.5, No.1, p.16-24 (2012)]

AIST succeeded in developing a circulatory assist centrifugal pump, which can be used as a bridge-to-bridge device of a period within four weeks before a long-term use of ventricular assist device. The adopted mechanism of monopivot bearing was originally proposed by AIST. As design verification, flow visualization was performed to evaluate the geometry and the in vitro antithrombogenic testing, proposed originally by AIST, was applied to evaluate the antithrombogenicity. And then, the animal testing was conducted in collaboration between medical and engineering teams. AIST not only succeeded in developing a product with original seeds, but also established and distributed engineering evaluation methods and the R&D guidance for industries.

Keywords : Artificial heart, centrifugal pump, monopivot bearing, flow visualization, in vitro antithrombogenic test

1 Historical background of R&D of artificial hearts

Population Statistics of the Ministry of Health, Labor and Welfare (MHLW) in 2010 indicates 350 thousand people died of cancer, 190 thousand died of heart disease, and 120 thousand died of brain/vessel disease. The second and the third causes sum up to 300 thousand people in total. Among them there are 195 heart transplantation nominees as the most serious patients. Even though the transplantation law was improved to include donors based on family agreement and the number of donors increased from 6 to 40, 150 donors are still lacking. The possible remedy for this situation is an artificial heart or regenerative medicine. However, in emergency cases, the artificial heart is the only choice for heart patients.

History of the artificial heart technology is as follows:

1) Initiation as the total replacement artificial heart with large-scale pneumatic pumps,

2) Change of the purpose from heart replacement to heart assistance (paracorporeal use),

3) Out-of-hospital pumps with implantable ventricular assist devices (VAD),

4) Reduction of size by using rotary blood pumps,

5) Durability enhancement with non-contact bearings: the maximum period of use at present is 7.5 years.

As surgical pumps

6) Roller pumps or centrifugal pumps are limited to one-day use,

7) The circulatory assist pumps with catheters are limited to one-week use,

8) A new category of care, bridge-to-decision, is emerging, which is used for 1 to 12 months before the implantation of a long-term VAD.

The history of the artificial heart is that of overcoming thrombosis and infections. Dr. Kolff and Dr. Akutsu initiated animal experiments of an artificial heart in 1957 at the Cleveland Clinic Foundation Hospital. It was not before the development of antithrombogenic materials in 1981 that a clinical study started for a total replacement artificial heart. The subsequent clinical applications moved to implantable ventricular assist devices (VADs) from 1987. It enabled patients to go out of hospitals and reached the number of 4600 cases. The first generation of VADs was mainly large-size pulsatile pumps which weighed more than 1400 grams.

Small-size rotary VADs were introduced in 1998 and an innovation occurred. They are called the second generation VADs, which use mechanical bearings. Clinical study for axial-flow pumps started in 1998 and the total number has reached 6500 up to now. Their merits are the small size for implantation, such as 200-500 g, and the reliability due to reduced number of components.

The second innovation occurred when they introduced non-contact bearings in combination with the rotary mechanisms. They are called the third generation VADs and their clinical study started in 2004. They are using the magnetic bearing, which levitates the impeller with position sensors and electromagnets, or the hydrodynamic bearing, which levitates the impeller with grooves on the surfaces accompanied by high pressure spots, or the mechanical seal, which block the invasion of blood with thin liquid films. Most of them are centrifugal pumps, which are featured with hyper durability

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Original manuscript received September 5, 2011, Revisions received December 13, 2011, Accepted December 20, 2011

Table 1. Purpose of use, driving mechanism, mission life, and product information of artificial heart/ circulatory assist device

Purpose of use	Driving mechanism	Mission life	Product information
1) Total replacement artificial heart	Pneumatic pulsatile pump	1 year (Endurance limit)	Jarvik 7 by Symbion
2) Paracorporeal ventricular assist device	Pneumatic pulsatile pump	1-12 months (Endurance limit)	Toyobo VAD by Nipro
3) Implantable pulsatile VAD	Electro-magnetic pulsatile pump	1 year (Endurance limit)	Novacor、HeartMate XVE
4) Implantable rotary VAD	Motor-driven rotary pump (mechanical bearing)	5 years or more (on going)	DeBakeyVAD=HeartAssist5、Jarvik 2000、HeartMate II
5) Implantable rotary VAD	Motor-driven rotary pump (non-contact bearing)	7 years or more (on going)	DuraHeart by Terumo, EVAHEART by Sun Medical Tech.Res., VentrAssist by VentraCor, HVAD by HeartWare
6) Surgical extracorporeal pump	Roller pump or Centrifugal pump	6 hours	BioPump by Medtronic, Capiox by Terumo, HPM15 by Senko Medical, etc.
7) Circulatory assist during/after operation	Centrifugal pump (mechanical bearing)	4 days	RotaFlow by Maquet, etc.
8) Bridge-to-decision (new category)	Centrifugal pump (non-contact bearing)	1-6 months	Not approved yet

though the size is a little larger than axial flow types. An axial flow pump with hydrodynamic bearings has also been developed by the National Cerebral and Cardiovascular Center (NCVC)/the National Institute of Advanced Industrial Science and Technology (AIST)/Mitsubishi Heavy Industries, Ltd./Nipro Corporation.

The second and the third generation VADs enabled patients to go out of the hospital. The controllers are portable and the batteries can be used for 8-10 hours, and the patients can use showers at home. The recent implantations of VADs are almost all rotary pumps in the US. The patients can return to their factories or campuses even in Japan.[1]

At present a necessary device for patients is a bridge-to-bridge pump applicable up to the next diagnosis such as the eligibility for implantable VADs or the sufficient recovery of lung function. However, the presently available product is a pneumatic ventricular assist device whose price is more than 30,000 US dollars. A circulatory support pump applicable up to four weeks is necessary whose price is less than 5,000 US dollars. We, at AIST, have been studying the second and the third generation VADs and, based on the research, have succeeded in developing a product for a circulatory support pump for four-week use. In the present paper we describe the scenario of the R&D process and the collaboration between the medical and the engineering teams (M/E collaboration).

2 Research of a monopivot centrifugal blood pump

When we started the research of artificial heart in 1991, rotary pumps for open heart surgery were requested to eliminate shaft and seal structure. Among seal-less pumps we proposed the "monopivot" mechanism[2] (Fig. 1), which supports the impeller on a point contact, had it patented and started collaboration with the School of Medicine of University of Tsukuba. The pump made by former technology was such that the pump impeller was supported with a shaft and two ball bearings and, therefore, it easily induced hemolysis or thrombosis due to the leakage of blood from the seal. A double pivot pump was also proposed by other facilities. Then we proposed a one-point support mechanism because it was expected to reduce the contact area as well as the hemolysis.

An important advice from the clinical side (Professor and Dr Tatsuo Tsutsui, University of Tsukuba) in the collaboration was that, saving animal experiments, engineering evaluation, or in vitro testing, should be conducted first to obtain scientific evidence and then we can proceed next to the animal experiment. It can be called a concept of evidence-based medicine. We joined the national project of NEDO totally implantable artificial heart which started in 1995 and set a tentative goal of developing an implantable VAD.

First, we repeated redesign and verification alternatively at each stage of the design through flow visualization. A visualized model was made with a 3 times scale-up acrylic model and the circuit was filled with 64 wt% NaI water solution (specific gravity: 1.9) whose refractive index (1.49) matches with the acrylic model. As tracer particles silver-coated glass beads (average size: 10 μm, specific gravity: 1.4) were used. The particle images were taken by a high-speed video system (Phantom), and were illuminated with Ar ion laser light sheet (output: 4 W). The images were analyzed with 4-frame particle tracking method for in-plane motion and with 3-frame particle tracking method for out-of-plane motion because the particle immediately disappeared. Centrifugal blood pumps are often provided with washout

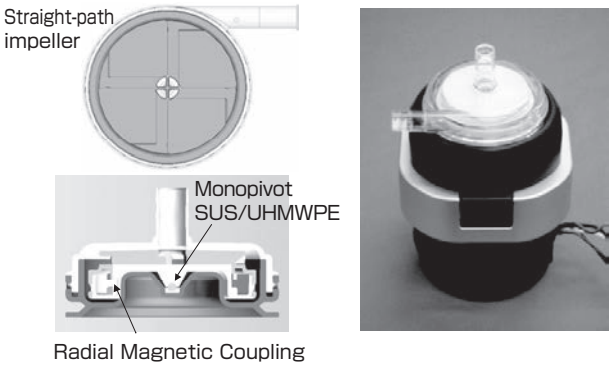


Fig. 1 Structure and picture of a disposable monopivot centrifugal blood pump as a product
(MERA centrifugal pump HCF-MP23, Senko Medical Instruments Mfg. Co. Ltd.)(Made of mainly polycarbonate, an impeller of 50 mm in diameter, a washout hole of 8 mm in diameter, a spherical pivot of 3 mm in diameter of a combination of a stainless ball and ultra high molecular weight polyethylene)

holes, penetrating the impeller to recirculate the fluid in a pump and to prevent thrombus formation, because the fluid behind the centrifugal impeller would not exchange automatically. The results of flow visualization verified that washout holes should be concentrated to a single hole with a small area compared to separate large holes[3] (Fig. 2).

Hemolysis testing using bovine blood revealed that the contact area governed the level of hemolysis; namely the smaller the contact area is, the lower the hemolysis level becomes[4] (Fig. 3).

Based on these evidences of flow visualization experiments and hemolysis testing animal experiments were conducted at University of Tsukuba, and the results were verified.

3 Reset of the goal of development based on clinical needs

When we were conducting animal experiments, a company, Senko Medical Instruments Mfg.Co.Ltd., joined the research collaboration. Generally medical device companies are often small/medium scale businesses, and they often join the development after animal experiments from the view point of risk management. Selecting AIST as a partner may be because the AIST team was not deeply connected to any companies then. Then the goal of development was switched from an implantable VAD of NEDO goal to a circulatory assist/extracorporeal pump for 4-week use based on the proposal of the company. The concept of monopivot centrifugal pump proposed by AIST was adopted for the product.

Clinically available blood pumps for cardiac surgery and cardiac assist at present can be classified into four categories as follows:

(1) Short term use (made of polymer, structure with seal, usable for 6 hours)
The pharmaceutical price is around 60,000 yen and the total number of production is 40,000 in Japan.
(2) Long term use (made of polymer, structure without seal, usable for 4 days)
The pharmaceutical price is around 100,000 yen though insurance does not cover the open-heart surgery use.
(3) Paracorporeal pulsatile VAD (placed outside the body, made of polyurethane, usable within a month)
The pharmaceutical price is 3,160,000 yen though the durability proof is within a month.
(4) Implantable VAD (made of Titanium, no limitation for period of use)
The pharmaceutical price is 18,100,000 yen and the insurance covers for implantation.

As an economic estimation, if an extracorporeal pump of 60,000 yen covers 25 % of the share of the market of 40,000 sales a year, the total sale would be 600,000,000 yen. In contrast, if an implantable VAD of 18,100,000 yen covers 50 % of the share of the market of 100 sales a year, the total sale would be 900,000,000 yen a year, which is almost the same as that of the extracorporeal pumps. Therefore, the former was selected as the goal of the development. The present pump features the cost of 60,000 yen and realizes a similar performance as the pneumatic VAD for one-month use of 3,160,000 yen. The goal of the product was set not only for surgical use but also for bridge-to-bridge use before long-term implanatble VAD, namely the performance is over (2) and the cost is (1).

The product of the monopivot centrifugal pump is composed of an impeller of 50 mm in diameter with straight paths, a monopivot bearing of a 3 mm sphere made of stainless steel/ ultrahigh molecular weight polyethylene, and a washout hole

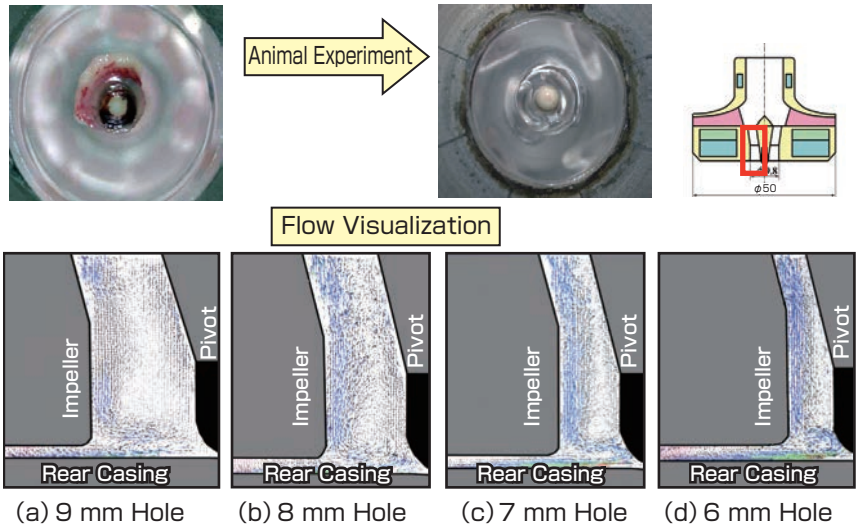


Fig. 2 Comparison of wash by washout hole through flow visualization for improvement of antithrombogenicity

of 8 mm in diameter. Though the pump is made mainly of the usual material, polycarbonate, the straight path structure and the assembling method without seals or adhesive materials are the original ideas of the company.

4 Role and fruits of AIST in the product design and the design verification

4.1 Engineering evaluation in the laboratory

Before the application to Pharmaceuticals and Medical Devices Agency (PMDA), the efficacy, safety, and quality designated in pharmaceutical law should be evaluated. The company was in charge of the evaluation of safety and quality. AIST was in charge of the evaluation of efficacy and conducted a flow visualization test, an in vitro thorombogenicity test, and a durability test for design evaluation.

The AIST empirical standard for thrombus formation is shear rate of less than 300 s^{-1}. As a result of flow visualization, since flow region of less than 300 s^{-1} was found at a sharp corner of the pivot support, a geometrical modification was performed for the corner[5][6] (Fig. 4).

In the durability test the impeller axial displacement was continuously measured with a laser confocal displacement meter. It was verified that the axial wear rate of the female pivot was as small as 1.1 μm/day. Though the geometry of the wear section generally becomes the letter W for rotational wear tests, the trace of wear was not observable. The operation was found to be sufficiently silent.

The in vitro thrombogenic test was proposed by AIST to investigate whether thrombus forms or not before animal experiments.[7] The closed circuit including a test pump was filled with purchased bovine blood, and sodium citrate and calcium chloride were used to maintain the active clotting time (ACT) to be around 200 s and the temperature at 37 °C for two hours. As a result of this method, the thrombus induced by a small difference of male/female pivot radii was successfully removed by adjusting the radii (Fig. 5).

4.2 Animal tests as M/E collaboration

We repeated more than 20 animal tests with sheep at University of Tsukuba with prototype blood pumps to eliminate thrombus and finally found no thrombus in a five-week animal experiment. The mass production models were also tested at Tohoku University and no thrombus were found in a 4-week animal test (Fig. 6). As mentioned above, the medical team advised us of the concept of evidence-based medicine, namely we do not go directly to multiple animal experiments but utilize *in vitro* testing to obtain scientific evidences. We conducted sufficient flow visualization experiments and *in vitro* thrombogenic tests and minimized the number of animal experiments. The important advice led to an efficient development and this can be regarded as the fruit of the M/E collaboration.

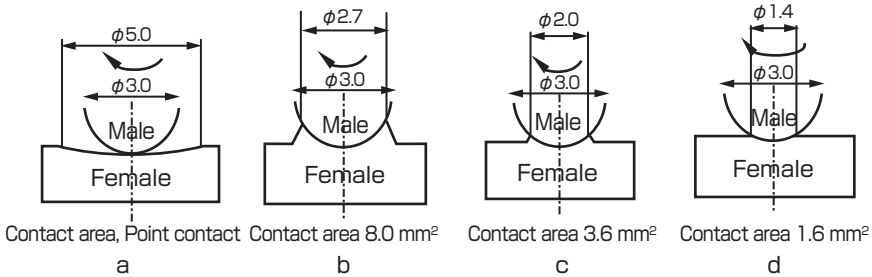
Generally speaking, M/E collaboration has two patterns. One is where a hospital supports a company to test a product based on a company's seed. This is because a company cannot be a user of medical products by itself. The other is where a university, a hospital, or a research facility offers a seed and a company joins to realize a product. The case presented in this paper corresponds to the latter case. Former cases of similar patterns for VADs are as follows and most of them are accomplished products:

a pulsatile VAD with pneumatic driver of Xeon Medical/ University of Tokyo

a pulsatile VAD with pneumatic driver of Toyobo/National Cardiovascular Center

a rotary VAD with a magnetic bearing of Terumo/Kyoto University

a rotary VAD with a mechanical seal of Sun Medical



Hemolysisi Indices of Monopivot Pumps (g/100L)

Geometry	Hemolysis Index	Hemolysis index of control	Relative ratio
a	0.001	0.003	0.3
b	0.010	0.003	3.3
c	0.012	0.004	3.0
d	0.002	0.002	1.0

Fig. 3 Difference of hemolysis levels due to difference of pivot geometries

Technology Research/Waseda University
a centrifugal blood pump of Nikkiso/Baylor Medical University
a centrifugal blood pump of Kyocera/Baylor Medical University

4.3 Summery of outcomes

As mentioned above, AIST conducted R&D mainly on the hemocompatibility and durability of the design. The monopivot centrifugal pump features:

1) Small wear, silent sound, durable over four weeks.
2) Thrombus free, low hemolysis, hemocompatible over four weeks.
3) The product can be offered with a low price as a surgical pump in addition to having the above performance.

The following AIST original technologies were useful in the development:

1) "Monopivot bearing" is a mechanism AIST proposed internationally.[2] Wear, hemolysis, and thrombus formation occur at the monopivot and it was theoretically and experimentally verified that the contact area has a close relation to them.[3] The hemocompatibility and the durability were verified to be effective over 4 weeks.
2) We proposed "flow visualization technique" which can predict quantitatively the hemocompatibility.[5][6] After our presentations flow visualization sessions were increased in international conferences and ISO 14708-5 adopted flow visualization as an ANNEX. As mentioned later the obtained data of the flow visualization was used as the application for the PMDA or for US Food and Drug Administration (FDA) and they were approved.
3) "*In vitro* thrombogenic test" was a method we proposed for evaluation of hemocompatibility before animal experiments.[7] Though this method is still under development, there are several companies doing collaborative researches with us.

On the other hand, the original technologies of the company were as follows:

1) Cost reduction by adopting an assembling method without seals or adhesive materials.
2) Cost reduction by removal of permanent magnets or ceramic components.
3) Inhouse manufacturing of a motor driving unit with a radial-flux magnetic coupling.

As a result, the equivalent function to a pneumatic driven VAD of 3,160,000 yen was realized with a centrifugal pump of around 60,000 yen. Furthermore, AIST inhouse program for patent application to a product was useful especially for establishing the business plan.

5 Outcome as a product

Senko Medical Instrument Mfg. Co. Ltd. started the collaboration research with us in 2002, submitted the pharmaceutical application at the end of 2008 regarding "MERA centrifugal pump (HCF-MP23)" and obtained the approval in January 2011. The pump was launched into the market in April 2011, and the total number of clinical applications was more than 100 at the end of November

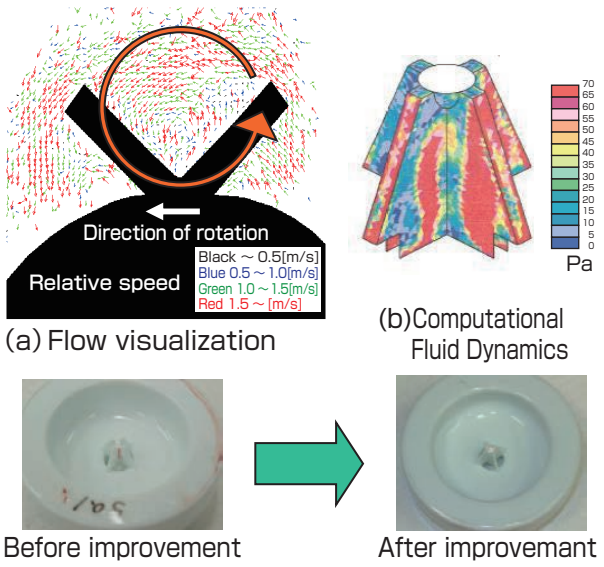


Fig. 4 Prevention of thrombus formation through flow visualization and computational fluid dynamic analysis
Elimination of thrombus formation by predicting thrombus at the corner of the pivot support

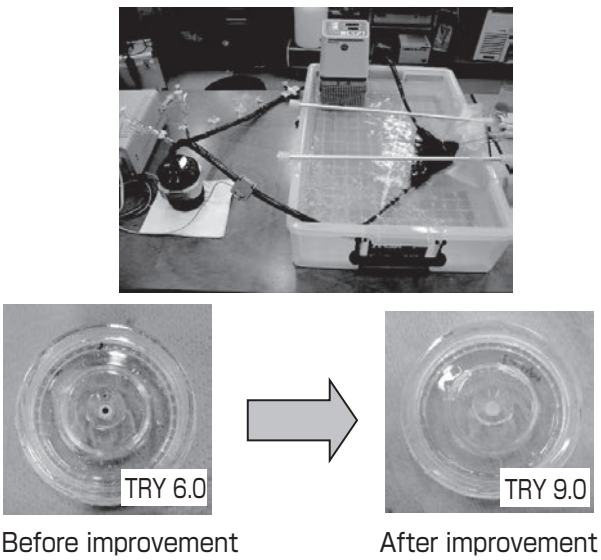


Fig. 5 Prevention of thrombus formation through in vitro thrombogenic test
The closed circuit including a test pump was filled with purchased bovine blood, and sodium citrate and calcium chloride were added to maintain the active clotting time (ACT) to be around 200 s and the temperature at 37 °C for two hours

2011. The approval covers an extracorporeal pump use for cardiovascular surgery and the name "MP23" denotes monopivot bearing, which shows the contribution of AIST. The pump features silent operation and less wear. The necessary time for development was 9 years. We kept the number of animal experiments low and accumulated sufficient engineering data which could become bases of design and could be used as descriptive material for users. Though the approved duration of use was 6 hours, AIST has done research to verify the durability and hemocompatibility for 4 week use, and therefore, it is expected to be used in the future for the new, bridge-to-bridge care before the implantation of a long-term artificial heart. Further collaboration with hospitals would expand the application field.

6 Future contributions of AIST to industries

Our research made contributions not only to a company product but also to other facilities or companies with our technology evaluation technique. AIST also made contribution to the Guideline Program of METI/MHLW to promote speedy approvals of medical devices for industries.

Among two implantable VADs approved in December 2010, we conducted flow visualization for EVAHEART by Sun Medical Technology Research and the data was submitted to premarket approval of PMDA and to the investigational device exemption (IDE) of FDA. The approvals have been successfully obtained. For DuraHeart of Terumo, we contributed to making VAD guidelines to establish a consensus for evaluating items and to shorten the review period.

Recently our research collaboration has expanded to overseas companies. AIST will make contributions to domestic and overseas industries using our development technology as well as our evaluating technology.

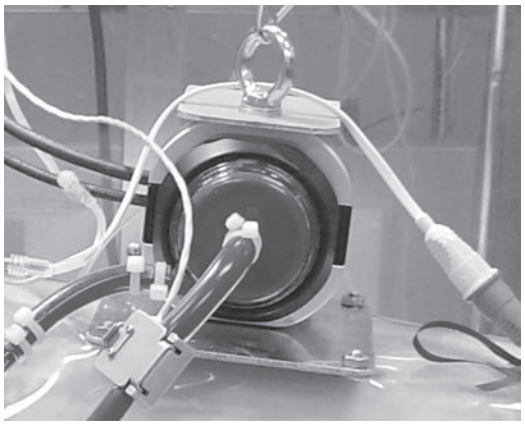


Fig. 6 Animal experiment using monopivot centrifugal blood pump
Conducted for 4 weeks at Tohoku University, paracorporeal application as left heart bypass

7 To the researchers who wish M/E collaboration

Our experience clarified that the followings are necessary for making a product in medical engineering.

1) Medical engineering researches are team studies which cover mechanics, fluid, material, and electo-mechanical engineering, as well as medicine, manufacturing, regulation, insurance reimbursement. The Japanese situation should be understood that instead of buyers the insurance pays for the devices based on the national health insurance.

2) The project should have research leaders who watch the project and connect different teams with each other for a long period, though the administrators may change, since the development needs roughly a decade. As the results or remedies of medical or engineering subjects appear at random, synthesizing the solutions into a system is similar to building with blocks. We kept steady M/E leaders for twenty years.

3) Research collaboration among a research institute, a medical facility, and a manufacturing company should be as equal partners. We see many cases where a medical team governs the project and where the project tends to do research instead of making products. However, balancing the purpose, design and materials is important to be accepted by the maximum number of patients. Therefore, the activity and the experience of the company should also be respected. The academia often tends to pay attention to a total replacement heart (TH) first, a VAD second, an extracorporeal pump third. The present case is a model case where the economic aspect was taken into account with assistance of academia or a research institute.

4) A good product goal should be made instead of a good research goal. AIST should seek for a goal of social needs instead of seeking its own research goal. Though obtaining research budget is important, "research for research sake" does not lead to social acceptance.

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Authors

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Discussions with Reviewers

1 Overall structure

Comment (Motoyuki Akamatsu: Human Technology Research Institute, AIST)

The purpose of *Synthesiology* is to publish papers that allow readers to gain knowledge of how to poceed with research. It is expected that the papers would explain, for example, at what timing of the research and development process the researcher decided on what was needed, to what the attention would be given and what were the reasons behind the decisions. With this in mind, in chapter 2, goal setting a goal is mentioned, but is it possible to write about the scenario of what kind of development was to be conducted for that goal?

Answer (Takashi Yamane)

In chapter 2, we explain the logic of research, and extract the important phenomena of designing for "2.Research of a monopivot centrifugal blood pump." In chapter 3, we point to the revision of target of product development as "3, Reset of the goal

of development based on clinical needs." We restored chapter 4 to cover the development results as it did originally.

2 Relevancy between design verification of the pump and experiments

Comment (Motoyuki Akamatsu)

At the beginning of subchapter 4.1, it is written that design verification was efficiently conducted to solve problems. Please explain why the flow visualization test and the in vitro thrombogenicity test were necessary so that the readers outside of the field may understand. Please explain the degree of advantage by comparing with the research and development of other pumps.

Question (Jun Hama: Energy Technology Research Institute, AIST)

In the chapter concerning design verification of the pump, the flow visualization test, the *in vitro* thrombogenicity test and the durability test are explained. What is the whole picture of design verification of pumps? Please write your response to each category of verification of the three tests in more detail.

Answer (Takashi Yamane)

I added the following to subchapter 4.1.

"Before the application to Pharmaceuticals and Medical Devices Agency (PMDA), the efficacy, safety, and quality designated in pharmaceutical law should be evaluated. The company was in charge of the evaluation of safety and quality. AIST was in charge of the evaluation of efficacy and conducted a flow visualization test, an in vitro thrombogenicity test, and a durability test for design evaluation."

These evaluation techniques were requested by the clinical side and I added what kind of effect there was in subchapter 4.2.

"As mentioned above, the medical team advised us of the concept of evidence-based medicine, namely we do not go directly to multiple animal experiments but utilize *in vitro* testing to obtain scientific evidences. We conducted sufficient flow visualization experiments and *in vitro* thrombogenic tests and minimized the number of animal experiments. The important advice led to an efficient development and this can be regarded as the fruit of the M/E collaboration."

Moreover, I added its effect in chapter 5.

"The necessary time for development was 9 years. We kept the number of animal experiments low and accumulated sufficient engineering data which could become bases of design and could be used as descriptive material for users."

3 Standard for approval of assist pump

Question (Jun Hama)

How is the standard of approval for assist pumps for cardiovascular surgical procedure stipulated?

Answer (Takashi Yamane)

Basically, there are standards for safety in pharmaceutical law; however there is no standard for efficacy. Efficacy is determined not by numerical evidence but by the duration of evidence (data taken during 6 hours in this case).

4 Development of evaluation technique

Question (Jun Hama)

How should we understand that the evaluating endpoints and verification experiment would be approved in Japan and overseas as a method of evaluation? For example, what kinds of measures are you taking in order that these methods of evaluation would be recognized more widely as a conventional evaluation technique rather than a specific evaluation method of artificial heart design?

Answer (Takashi Yamane)

We included visualization tests in the evaluation method of the artificial heart of ISO. Evaluation methods vary depending on how far the companies want to file. Examples are explained in chapter 6. In December 2010, we conducted flow visualization for EVAHEART by Sun Medical Technology Research and the data was submitted to premarket approval of PMDA and to the investigational device exemption (IDE) of FDA.

5 Decision for productization and resetting of target

Question (Motoyuki Akamatsu)

One of the points of this paper is the decision made when Senko Medical Instrument Mfg. Co. Ltd. joined the research aiming for productization and the resetting of the target later. Although there must have been many other researches for artificial hearts, please write the reason why this company chose to commercialize this monopivot centrifugal pump, or why it saw the possibility of productization.

Question (Jun Hama)

It can be presumed that the difficulty of productization related to medical fields is the reason why the target to develop an artificial heart in collaboration with a university was changed to extracorporeal circulatory pump in the productization efforts with a company. Would you explain to us the reason for that change in detail?

Answer (Takashi Yamane)

The reason for the decision the company made for the productization of monopivot centrifugal pump was based on an introduction by a university professor who was a research partner of the monopivot centrifugal pump development. There were only five groups which had reached animal experiments among the institutes researching rotatary type artificial hearts in 2002.

It seems to me that among these groups, only AIST was in a position where the company could easily participate in.

We mentioned the process of resetting the development target in chapter 3. Doing business with inexpensive, low-risk products or disposable products is the basic stance of the collaborating company. This company can easily procure polymer material and is good at processing it. With our design, it assembles the pump with little adhesive, using a cheap manufacturing method that does not use O ring or screws often used for ordinary products. There was a prospect that, if the monopivot mechanism of AIST was used, an inexpensive product without ball bearings and shaft seals could be made. That was the reason for aiming at productization of a circulatory assist pump based on the AIST's method.

6 Medicine-engineering collaboration

Comment (Motoyuki Akamatsu)

Concerning medicine-engineering collaboration, as of medicine, there is the basic research point of view of medical doctors of research and the clinical view from treatment and diagnosis of patients at hospitals. As for engineering, there are university professors and researchers of public research institutions in the field of engineering, and engineers involved in productization at companies. I think if you can organize the parties involved, it would be of use to the readers.

Answer (Takashi Yamane)

There are usually two types for the medicine-engineering collaboration. One is where a company and a hospital collaborate as a manufacturer and a user, to realize a product because the law prohibits medical device manufactures from being users themselves, which is different from general industry. The other is where universities, hospitals or research institutions offer seeds and companies join them to realize productization according to the needs. The case presented in this paper is the latter case. I added the examples of successful productization of artificial assist hearts (VAD) in subchapter 4.2.