厚生労働科学研究費補助金
医療機器開発推進研究事業

循環器病治療機器の医工連携による研究開発・製品化・汎用化を実現するための基盤整備に関する研究（H20-医工-一般-002）

平成２２年度　総括・分担研究報告書

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平成２３（２０１１）年４月

２／２冊

Artificial Organs

Artificial Organs
34(9):699–702, Wiley Periodicals, Inc.

Japanese Guidance for Ventricular Assist Devices/Total Artificial Hearts

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Abstract: To facilitate research and development (R&D) and to expedite the review processes of medical devices, the Ministry of Health, Labor and Welfare (MHLW) and the Ministry of Economy, Trade and Industry (METI) founded a joint committee to establish guidance for newly emerging technology. From 2005 to 2007, two working groups held discussions on ventricular assist devices and total artificial hearts, including out-of-hospital programs, based on previous guidance documents and standards. Based on this discussion, the METI published the R&D Guidelines for innovative artificial hearts in 2007, and in 2008 the MHLW published a Notification by Director regarding the evaluation criteria for emerging technology. **Key Words:** Guidance—Evaluation criteria—Ventricular assist device—Total artificial heart.

Although heart transplantation and artificial heart implantation are two complementary approaches for severe heart disease, the number of donor hearts is limited in Japan. The total number of registrations for heart transplantation was 159 over the past 12 years, while only 70 donors were found in Japan, with an average of five to six a year. Recent innovations in artificial hearts, on the other hand, particularly in reducing the pump size and in developing noncontact bearings, have enabled devices to be implanted and have allowed patients to be discharged home. Artificial hearts are applicable as bridge-to-transplantation (BTT), bridge-to-bridge, bridge-to-recovery (BTR), or destination therapy (DT). Devices for DT, particularly those for long-term home care, will be necessary in the near future. However, in Japan there has been a device lag of several years compared with the USA from the application to the approval of medical devices. To this end, the necessity has been recognized not only for promotion of research and development (R&D) for these devices among academia and industry, but also for the establishment of guidance for R&D and for clinical evaluation.

There have been several previous guidance documents and standards for ventricular assist devices (VADs) and total artificial hearts (TAHs): the Food and Drug Administration (FDA) Guidance for VAD/TAH (1), the National Institutes of Health Request for Proposal for TAH (2), the American Society for Artificial Internal Organs (ASAIO)--Society of Thoracic Surgeons (STS) Reliability Recommendation

doi:10.1111/j.1525-1594.2010.01091.x

Received March 2010; revised June 2010.

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Presented in part at the 17th Congress of the International Society for Rotary Blood Pumps held October 1–3, 2009 in Singapore.

for Mechanical Circulatory Support Systems (3), The Association for the Advancement of Medical Instrumentation Technical Information Report for VAD/TAH (4), the Japanese Society for Artificial Organs Guidance for Clinical Trials (5), the Reliability Recommendation by the National Clinical Trial Initiative Subcommittee (6), and International Organization for Standardization (ISO) 14708-5 on Circulatory Support Devices as Active Implants (7).

To facilitate R&D and to expedite the review processes of medical devices, the Ministry of Health, Labor and Welfare (MHLW) and the Ministry of Economy, Trade and Industry (METI) founded a joint committee to establish guidance for newly emerging technology. Under the joint committee, two working groups were formed to establish Japanese guidance for VAD/TAH. The members of the committee represented the Japanese Association for Thoracic Surgery and the Japanese Society for Artificial Organs. From 2005 to 2007, the two working groups, chaired by Dr. S. Kyo and Dr. H. Matsuda, respectively, held discussions that referred to (i) previous guidance and standards; (ii) the results of a questionnaire on an out-of-hospital VAD program for domestic hospitals; and (iii) a survey on out-of-hospital VAD programs through a mission to US hospitals and universities. Based on this discussion, the METI published the R&D Guidelines for innovative artificial hearts (8) in 2007 and the MHLW published a Notification by Director in 2008 regarding the evaluation criteria for emerging technology (9,10).

R&D GUIDANCE

The R&D Guidance, published as METI R&D Guidelines for innovative artificial hearts (8), is composed of the following items:

1 Purpose of use: The present guidance covers left/right ventricular assist devices, biventricular assist devices, and TAHs for bridge and destination therapy.
2 Human factors and environments: There should be no adverse events during transportation or exercises. No adverse events in any environment during air travel or computed tomography. No impingement or necrosis of surrounding tissues. Allowable level of noise/vibration. Usability should be considered for controllers and batteries. Alarms should satisfy the International Electrotechnical Commission (IEC) 60601-1-8.
3 Fluid dynamic characteristics: Nonpulsatile pumps should satisfy ISO 5198 and pulsatile pumps ISO 4409. Supplemental information can be introduced by numerical analyses and/or flow visualizations.
4 Heating characteristics: There should be no adverse events on surrounding tissues caused by hot spots. The temperature rise should satisfy ISO 14708-1.
5 Electronic safety: The device should satisfy IEC 60601-1 and ISO 14708-1.
6 Electromagnetic compatibility: The device should satisfy IEC 60601-1-2 and IEC CISPR-11.
7 Control and monitoring: Device should be able to keep intended flow and flow stability and be implemented with necessary limiters and with necessary monitors.
8 Conduits, grafts, artificial heart valves, or heart cuffs: The conduits should be evaluated with ISO 7198 and the valves with ISO 5840. The conduits, grafts, or heart cuffs should not induce stenosis or cause air sacks. Junctions should be evaluated against tension, twist, vibration, kink, or leakage.
9 Materials safety: The device materials should be evaluated with ISO 10993-1.
10 Biocompatibility: The device biocompatibility should be evaluated with ISO 10993-1, ISO 10993-4, and ASTM F1841-97.
11 Animal testing: There should be no severe thrombosis caused by the device. The sample size should be at least six animals and the duration 60 days. Whether a test involving more than eight animals and 90 days is necessary should be considered from the point of international harmonization.
12 Durability (Reliability): The reliability tests should be conducted with 80% reliability, 60% confidence level (80% is preferable), and a period of 6 months, to be extended to over 2 years. Test conditions such as flow and pulsatility should be defined in advance.

Annex A. Supplement for TAH: Common factors and discrepancies between TAH and VAD.

Annex B. Supplement for durability test: Test conditions should reflect the patient's physiological conditions and lifestyle. Handling rules for various events should be defined in advance.

Annex C. Supplement for out-of-hospital program: Requests for organizing a medical team for VAD; for establishing a training system for patients and caregivers; for establishing discharge criteria; for clarifying the emergency system to patients, caregivers, the medical team, and the ambulance system; for arranging a monitoring system; and for arranging a device maintenance system.

CLINICAL EVALUATION GUIDANCE

The clinical evaluation guidance, published as MHLW Notification by Director (9), is composed of the following items:

1 Fundamentals: Human factors and environments
2 Nonclinical evaluation
  In vitro evaluation (including Annex 1)
  In vivo evaluation (including Annex 2)
3 Clinical evaluation
  3.1 Compliance with good clinical practice
  3.2 Clinical trial protocol
    3.2.1 Fundamentals: End points, other treatments, control, informed consent, patient management/follow-up, out-of-hospital program (Annex 3), training program for medical and co-medical staff, data safety monitoring board, criteria for discontinuing the clinical trial, etc.
    3.2.2 Applicable diseases: End-stage cardiac diseases as defined by the Japanese Circulation Society.
    3.2.3 Objectives: BTT, BTR, or DT.
    Inclusion criteria: Patients with end-stage heart disease with extremely low quality of life (QOL).
    Exclusion criteria: Severe infection, irreversible multiorgan failure, pregnancy, complications of chronic pulmonary disease, pulmonary thrombosis, or pulmonary hypertension, etc.
    3.2.4 Sample size and duration: Overseas data allowed. End points suitable for the feasibility study or the pivotal study (Annex 4).
    3.2.5 Facility qualification (Annex 5)
    3.2.6 Data acquisition rules
    3.2.7 Adverse events
    3.2.8 Safety evaluation
    3.2.9 Final evaluation (Annex 6)

Annex 1. Durability test (Same as R&D guidance section 12)

Annex 2. Sample size and duration for animal testing (Same as R&D guidance section 11)

Annex 3. Out-of-hospital program (Same as R&D guidance Annex C)

Annex 4. Sample size and duration for clinical trials: Recommendations for clinical trials are around five cases for a feasibility study and around 15 for a pivotal study. The recommendations for end points are 3 months for the feasibility study, and, in a pivotal study, 6 months for BTT and 12 and 24 months for DT.

Annex 5. Facilities for clinical trials: Institutions certified as VAD facilities that perform more than 100 cardiac surgeries a year. VAD implantation experiences for more than five cases. They should have adequate transplantation facilities or be closely affiliated with these. Staff members must have finished a training course and there must be a committee including a cardiologist. The procedure should be switchable to paracorporeal VAD.

Annex 6. Final evaluation: (the Global Harmonization Task Force [GHTF] SG5/N1R8 and SG5/N2R8) For bridge VAD (BTT and BTR), clinical evaluation should be conducted (i) when patients remain alive for more than 6 months with satisfactory QOL, (ii) in the case of heart transplantation within 6 months, or (iii) in the case of recovery within 6 months. For DT VAD, clinical evaluation should be conducted (i) when patients remain alive for more than 12 months with satisfactory QOL, (ii) in the case of heart transplantation within 12 months, or (iii) in the case of recovery within 12 months. For TAH, clinical evaluation should be conducted when patients remain alive for more than 2 months with satisfactory QOL.

DISCUSSION

Table 1 shows a comparison between historical guidance and standards. Regarding reliability testing, the FDA guidance (1) requested that X or more devices are used with less than Y failures over twice the intended use for short-term use and over Z years for long-term use. The ASAIO-STS (3) required 80% reliability with at least 60% confidence for 1-year mission life. The National Clinical Trial Initiative Subcommittee (6) required the same level before Investigative Device Exemption (IDE). The ISO/DIS requires that a reliability of X with at least Y confidence for a Z-year mission life is described. The Japanese guidance requires 80% reliability with at least 60% (80%) confidence for 6 months, similar to the ASAIO-STS recommendation.

Regarding animal testing, the FDA (1) required a duration of 5 months. The ASAIO-STS reduced the request to eight animals for 90 days before IDE. The ISO/DIS requires only that the sample size and duration are described. The Japanese guidance reduced the request to at least six animals for 60 days with consideration of eight animals for 90 days if necessary, which is a small reduction from the ASAIO-STS recommendation.

Regarding clinical trials, the Japanese guidance referred to practical goals for a feasibility study and for a pivotal study, although most guidance

TABLE 1. *Comparison of historical guidance documents and standards for VAD/TAH*

	Japanese R&D guidance (8) & Clinical evaluation guidance (9)	ISO 14708-5 (7)	Reliability recommendation by National Clinical Trial Initiative Subcommittee (6)	ASAIO-STS Recommendation (3)	FDA guidance (1)
Reliability test (in vitro)	80% reliability with 60% (80%) confidence for 6 months (to be extended ≧2 years).	Reliability X with at least Y confidence for a Z year mission life.	Reliability R for mission duration T and confidence C* For destination therapy 80% reliability for 1 year with 60% confidence before IDE. The study is not ended until failures have been accumulated.	A calculated 80% reliability with at least 60% confidence for 1 year mission life. Before IDE ≧ 8 systems for ≧1 year.	≧X devices with ≤Y failures. *Short term*: over ≧twice the intended duration. *Long term*: over ≧Z years.
Animal test (in vivo)	At least six animals for 60 days (eight animals for 90 days).	Sample size and implant duration appropriate for demonstrating the safety and performance for the intended use.		IDE**: In a minimum of 8 animals for 90 days	Durability and performance for ≧twice the expected duration. Permanent implant device for ≧5 months.
Clinical trial	*Sample size*: Around 15 cases for a pivotal study (around 5 cases for a feasibility study). *End point*: 3 months for a pilot study, 6 months for BTT, and 12 (and 24) months for DT for a pivotal study.	ISO 14155-1 and ISO 14155-2		PMA***: All in vitro, in vivo, and clinical data reported by category • The number of patients; • The number of patient-years.	A rationale for the number of patients and institutions required for the conclusions about the safety and efficacy (Preliminary IDE study: 5–10 patients at 1–2 centers)

* Ex.1. If eight systems for 1 year with no failure, 80% confidence for 80% devices not to fail for 1 year. Ex.2. If 15 systems for 1 year with one failure, 80% confidence for 80% devices not to fail for 1 year. ** IDE: Investigational Device Exemption.
*** PMA: Premarket Approval.

documents and standards do not refer to practical periods. The present guidance is expected to contribute to the clinical application of VAD/TAH in Japan.

CONCLUSIONS

The R&D guidance and the clinical evaluation guidance were established through collaboration between academia, industry, and government. Such collaboration is very important, not only for artificial hearts but also for all newly emerging medical devices. Since the present article is an overview presented by the authors and is not an authorized guidance by the MHLW or PMDA, it is recommended that readers refer to the original guidance.

Acknowledgments: The introduction of guidance is funded by the METI Introduction Program of R&D Guidelines for Medical Devices and the MHLW Introduction Program of Evaluation Criteria for Newly Emerging Medical Devices.

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J Artif Organs (2010) 13:1–9
DOI 10.1007/s10047-010-0497-9

REVIEW

Journal of Artificial Organs 2009: the year in review

Journal of Artificial Organs Editorial Committee

Received: 18 February 2010 / Published online: 24 March 2010

Introduction

Members of the Editorial Committee of the *Journal of Artificial Organs* (JAO) are pleased to introduce to colleagues worldwide through the publication of JAO a broad spectrum of important new achievements in the field of artificial organs, ranging from fundamental research to clinical applications. We believe that the JAO has very high potential for promoting interest and research in artificial organs not only in Japan but in other parts of the world, and the specialization, originality, and level of science of the journal are at the highest levels in the field. An electronic version of the JAO has also been available through our publisher's electronic publishing system since 2002. The full text journal is accessible at more than 4000 institutes and libraries in the world. Beginning with Volume 1, papers from 18 countries have been accepted for publication, and the number of cited JAO articles in other journals has also been dramatically increasing. In 2008, JAO was accepted for abstracting and indexing in the Web of Science/Citation Index Expanded, and the first Impact Factor will be available in the middle of 2010. Four years ago we started reviewing and summarizing all the articles published in the previous year in the JAO in order to

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facilitate an overview for our readers [1–4]. We are continuing this practice this year as well, and we have summarized below the articles published in Volume 12, 2009. Volume 12 of the JAO published 44 articles including 25 original papers, 8 review papers, 3 minireviews, 3 case reports, 4 brief communications, and 1 technical forum paper related to the many aspects of the basic research, development and clinical applications of artificial organs. These included articles on artificial heart, cardiopulmonary bypass, artificial lung, blood vessel prosthesis, artificial valve, dialysis, artificial kidney, biomaterials, tissue engineering, regeneration therapy, and other topics. We are pleased to present such excellent work in our journal. For Volume 12, we had a total of 59 reviewers who are specialists in the field of artificial organs. We offer our profound gratitude to our reviewers for their thoughtful reviews, critiques, and suggestions, which help our authors to improve the work they submit for publication.

Artificial heart (basic)

One original paper, and a brief communication in the field of basic research of artificial hearts were published in 2009. These articles include important information about significant peripheral technology to develop cardiovascular support systems.

Tamura et al. of the Tokyo University of Science introduced the unifying transcutaneous transformer for simultaneous transmission of energy and information with a single transformer for a totally implantable artificial heart. They intersected perpendicularly the electromagnetic fields generated from the transformer windings for the energy and information transmissions to suppress the electromagnetic coupling between energy and information transmission. The developed unified transcutaneous transformer for the simultaneous transmission of energy and information indicated sufficient performance experimentally [5].

Masuzawa et al. of Ibaraki University presented the effect of hydraulic force, estimated by computational fluid dynamics (CFD) simulation, on magnetically levitated (maglev) pumps to certify the suspension performance of the pumps. Transient CFD analysis was performed to estimate the hydraulic force on the levitated impeller. The analysis revealed that the direction of the radial force changed dynamically as the vane's position changed relative to the outlet port during one circulation, and the magnitude of this force was about 1 N. Transient CFD analysis is not only useful for observing dynamic flow conditions in a centrifugal pump but is also effective for obtaining information about the levitation dynamics of a maglev pump [6].

Artificial heart (clinical)

A minireview, three original papers, and two case reports in the field of clinical research of artificial hearts were published in 2009.

Saito et al. reported a bridge-to-transplant case supported with a Toyobo left ventricular assist system (LVAS). The patient had cannula-exit site infection, which was appeared to have been overcome with conservative treatment. However, at the time of transplant, they found an abscess around the left ventricular apical cuff, which was successfully treated with orthotopic heart transplant and omentopexy. Exit site infections of LVAS patients should be followed very carefully [7].

Saito and his co-workers reported their 15-year experience with the Toyobo LVAS used as a bridge to transplantation or a bridge to recovery. The 1-year survival rate had improved to 45.9% in recent years, but there was still a significant morbidity rate especially for long-term support [8].

Ueno and Tomizawa of Tokyo Women's Medical University extensively reviewed cardiac rehabilitation in the clinical artificial heart field. They describe the concept of rehabilitation followed by cardiac rehabilitation for patients with heart failure, patients after open-heart surgery, and patients with implanted left ventricular assist devices (LVADs). They concluded that cardiac assist devices can be implanted at only a limited number of facilities in Japan. When the number of implantations increases, the level of medical treatment will advance. For patients with heart disease, cardiac rehabilitation can be used as an adjunct to both invasive and noninvasive treatments, and improvements in quality of life (QOL) and prognosis are expected [9].

Scherer et al. of J.W. Goethe University, Germany, demonstrated the effectiveness of extracorporeal membrane oxygenation (ECMO) for patients with cardiogenic shock to stabilize organ function prior to LVAD implantation. Five patients in cardiogenic shock were supported with ECMO before LVAD implantation. All patients were transferred to LVAD and the ECMO–LVAD interval was 8 ± 4 days. Overall survival was 80%. To avoid right ventricular failure, the ECMO was not removed at the time of LVAD implantation and was used as a right heart support. The authors concluded that ECMO support can immediately stabilize circulation and provide organ perfusion in patients with cardiogenic shock. To avoid RV failure, the ECMO should not be removed at the time of LVAD implantation [10].

Neumann et al. of the University of Essen, Germany, investigated whether a new percutaneously inserted system, which allows continuous aortic flow augmentation (CAFA), could be shown to be clinically effective with neurohormonal benefit in patients admitted with decompensated heart failure. Five acute heart failure patients were treated with a CAFA system made up of a centrifugal pump, a 12 F inflow cannula positioned in the left iliac artery, and a 12 F outflow cannula positioned through a right femoral arterial sheath terminating just below the subclavian artery level. The CAFA system was driven at a flow rate of 1.0–1.5 l/min. Brain natriuretic peptide (BNP) levels after CAFA treatment were decreased in all patients. None of the patients died or experienced severe adverse events [11].

Adachi et al. of the Osaka University Graduate School of Medicine reported on management of critical myocardial abscess resulting from cannula exit-site infection by LVAD replacement and omentopexy following extensive debridement of infected myocardial tissue. The best management for this condition is urgent heart transplantation. However, because of the severe shortage of donors, replacement of the infected LVAD might be an option that could save patients who otherwise would not survive [12].

Cardiopulmonary bypass

Accidents in cardiopulmonary bypass operations can be very serious problems and have begun to receive public attention recently. In 2009, we published one review, one original, one brief communication, and one technical forum contributions on cardiopulmonary bypass. Three of them discuss the training process or troubleshooting procedures for perfusionists.

Kenmoku published a review for practical simulation training for troubleshooting the heart–lung machine. Trouble in operating the machine is rare but could be lethal. Kenmoku showed from his experience, as well as with a literature review, that simulation training for such problems is very useful as preparation for handling them properly [13].

For patient safety, the perfusionist should be ready to prevent any accidents, and for that, education is important. Tomizawa from Tokyo Women's Medical University, Tokyo, reported the distribution of certified perfusionists as of 2008 in Japan, finding that 18 of 93 (19.4%) core institutions without certified perfusionists are university hospitals: 16 are the main hospitals of medical schools and 2 are branch hospitals. Additionally, 3 university hospitals accredited by the Japanese Board of Cardiovascular Surgery as affiliated institutions have no certified perfusionist [14]. The Committee for the Education of Japanese Society on Artificial Organs believes that the teaching of safety with respect to extracorporeal circulation technique is important [15].

Takahashi et al. of Osaka City University investigated the clinical efficacy of a new non-di-(2-ethylhexyl)phthalate (DEHP) bilayer tube. Sixteen patients undergoing coronary artery bypass grafting were randomly assigned to the non-DEHP bilayer group (group B, $n = 8$) or to the noncoated PVC group (group N, $n = 8$), and the blood levels of DEHP, interleukin-6 (IL-6), D-dimer, and thrombin–antithrombin complex (TAT) were measured before and after cardiopulmonary bypass (CPB). As a result, DEHP, IL-6, and D-dimer levels were significantly lower in group B after CPB compared with group N. The authors concluded that the use of this new bilayer tube had implications for developing a new method to minimize the influence of DEHP exposure on the human endocrine system while maintaining biocompatibility [16].

Blood vessel prosthesis

Major topics in blood vessel prosthesis in the past decade have been the development of a scaffold structure using electrospinning in basic research, and clinical use of both stent grafts and coronary stents. The vascular characteristics with an electrospinning method could be excellent with regard to physical properties and biocompatibility. In clinics, although the results from a randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms were reported, long-term follow-up is still needed to determine whether this advantage is sustained. Angiographically proven late stent thrombosis is still controversial in patients treated with a drug-eluting stent.

Nishi from Sapporo Higashi-Tokushukai Hospital, Sapporo, developed a self-expanding stent graft covered with an expandable segmented polyurethane (SPU) membrane with micropores and a drug delivery system. Micropores were formed, and then an argatroban coating was added. An in vivo study was performed to compare the developed stent graft and the bare self-expanding stent as a control using experimental canine aneurysms in the carotid artery position. Complete occlusion of aneurysms was accomplished by the developed stent graft [17].

Stents are currently in wide use in cardiovascular medicine. Hanawa from Tokyo Medical and Dental University, Tokyo, reviewed metals used for metallic stents. From the viewpoint of material engineering, the desirable properties and characteristics of metals are presented, and problems and disadvantages related to metallic stents are discussed. Also, metals including stainless steel, nickel–titanium alloys, tantalum, cobaltchromium alloys, and magnesium alloys are explained [18].

Artificial valve

With regard to basic and clinical research on the artificial valve, we published four original articles and one case report in 2009.

Bagno et al. [19] from the University of Padua, Italy, reported phonocardiographic analysis of bileaflet mechanical heart valve (MHV) closing sounds. Five commercial bileaflet MHVs (On-X, CarboMedics Top Hat, Sorin OverLine, Medtronic Advantage, and St. Jude Medical Regent valves) were studied under different conditions that were simulated in vitro using a Sheffield pulse duplicator for the aortic position. The closing sounds were captured by means of a phonocardiographic apparatus and were analyzed by a specifically implemented algorithm. They showed two patterns of the spectra of tested valves: the spectra of On-X, CarboMedics Top Hat, Sorin OverLine valves were centered on ±12 kHz, and the St. Jude Medical Regent and the Medtronic Advantage valves were centered on ±17 kHz. They also applied statistical analysis to the spectra of the MHVs acquired for different heart rates (60, 70, 80, 90, and 100 bpm). The On-X, the Medtronic Advantage, and the St. Jude Medical Regent valves were characterized by the highest reproducibility under the examined experimental conditions. They concluded that by investigating the spectral features of the closing sound it is possible to identify the typical "fingerprint" of each MHV.

Sugiki et al. [20] from the Hokkaido University Graduate School of Medicine reported a new automated wavelet analytical system with a cellular phone for recording intercellular phone remote transmitted bileaflet valve sound. They developed a continuous wavelet transform (CWT) using the modified Morlet wavelet (Morlet CWT) to detect the split interval (SI) of the closing sound of normally functioning bileaflet valves (NBVs), and in 2008 they reported that the signal analysis method using the Morlet CWT could be a useful tool to screen the function of bileaflet valves (BLVs) in a clinical situation. However, this system was difficult to apply to testing of bileaflet valve function in routine clinical practice because of limitations concerning both BLV sound (BLVS) recording and analysis procedures. To resolve the technical difficulty, they refined the analytical system and introduced a cellular phone for collecting and recording BLVS. They also developed a system of intercellular phone remote transmission of BLVS (ICTB). Remote transmission of BLVS was carried out between a patient's cellular phone and the doctors' cellular phone. They analyzed 51 St. Jude Medical bileaflet valves in 36 patients. The new system showed great improvement over the original system by simplifying BLVS recording and reducing analysis time by approximately 65%. ICTB also proved to be a useful BLVS recording method.

Oda et al. [21] from the Kurume University School of Medicine reported nonstructural dysfunction of a Carpentier–Edwards pericardial (CEP) bioprosthesis in the mitral position due to pannus overgrowth 9 years after implantation. During surgery, excessive pannus overgrowth was seen on the left ventricular side of the CEP bioprosthesis. Pannus encroachment on the leaflet caused poor coaptation of the bioprosthesis.

Lee et al. of the National Cardiovascular Center and Osaka University compared three kinds of bileaflet artificial valves, a 21-mm ATS valve, a 21-mm St. Jude valve, and a 21-mm Sorin Bicarbon valve, mounted in their pneumatic ventricular assist device, by downstream visualization of the outlet valve using the particle image velocimetry (PIV) method. As a result, the maximum flow velocity of the Sorin Bicarbon valve was shown to be less than that of the other two valves; however, it decreased slightly with increasing distance in the X–Y plane in all three valves. The authors concluded that the geometry of the leaflet was an important factor when selecting a bileaflet mechanical heart valve for use in an artificial heart [22].

Lee et al. of the National Cardiovascular Center investigated cavitation pits formed on the inlet valve (Medtronic Hall valve) surfaces of both the left and right blood pump of their electrohydraulic total artificial heart during in vivo testing. The presence of cavitation was determined by observation of cavitation pits on the explanted valve surfaces in three sets of valves used in four animals. They found that the longer the time of pump operation, the larger the cavitation pit number and size tended to be. A high driving pressure slope corresponded to an increase in the size of the area in which cavitation pits were observed. The authors concluded that, when estimating cavitation intensity in in vivo testing, both a high driving pressure slope and operational time are important factors [23].

Biomaterials

One review article, an original article, and a brief communication were published in the field of biomaterials in 2009.

Because synthetic polymer materials elicit severe inflammatory reaction when they are applied to the cover films of stents, much effort has been concentrated on finding a new method to prevent the outgrowth of smooth muscle cells. Nagai et al. of the Creative Research Institute "Sousei," Hokkaido University, developed self-expandable or balloon-expandable covered stents with a biodegradable salmon film. The covered stents were fabricated in two steps: gelation of salmon-collagen solution on the stents and subsequent lyophilization. They first implanted

the balloon-expandable covered stents in the common carotid arteries of beagles for 1 month. Their findings showed that all stented arteries were patent with no significant neointimal thickening [24].

Tanaka et al. observed differences of platelet adhesion and its spreading and the formation of fibrin network depending on types of metal oxide. Surface oxide films containing Cr_2O_3 on SUS316L and Co–Cr–Mo showed less adhesion than those of TiO_2 on Ti–6Al–4V, Ti–6Al–7Nb, and Ti. It is deduced that more albumin adsorption owing to a lower relative permittivity of Cr_2O_3 causes less platelet adhesion and the formation of a fibrin network [25].

For retinal prostheses Matsuo et al. developed polyethylene films coupled with photoelectric dye molecules, 2-[2-[4-(dibutylamino)phenyl]ethenyl]-3-carboxymethyl-benzothiazolium bromide, which converts photon energy to electrical potentials. In this review article, preparation of a photoelectric dye-based retinal prosthesis is briefly mentioned, followed by safety considerations as well as in vitro and in vivo evaluation [26].

Tissue engineering

The combination of artificial organs and tissue engineering will become an indispensable choice in new treatment technology. In 2009, we had seven original articles in the field of tissue engineering.

Miskon et al. of the National Cardiovascular Center Research Institute reported the effect of extracellular matrices on beating duration and cardiac-differentiation of cells. Beating of the isolated rat neonatal cardiomyocytes was strong and it continues for a long period of time on gelatin matrices. Interestingly, not only the beating duration but also the cardiac-differentiation of P19.CL6 into cardiomyocytes was strongly improved on the gelatin. This finding is useful for preparing cardiomyocytes as a source for cell transplantation therapy [27].

Yuan et al. of Shanghai Jiao Tong University reported the effects of genistein on rodent renal mesangial cells cultured in high glucose. The expression levels of type IV collagen, fibronectin, and TGF-b were studied because these proteins are considered to be harmful to the renal glomerulus if they are overexpressed by mesangial cells. They found that high glucose concentration enhanced type IV collagen, fibronectin, and TGF expression, while high concentrations of genistein inhibited their synthesis. This inhibition of the protein secretion by genistein may be beneficial to renal glomeruli in diabetic nephropathy [28].

Nieuwoudt et al. of the University of Pretoria, South Africa, succeeded in quantitatively observing the functionality of hepatocytes in bioreactors using positron emission tomography (PET). Because such bioreactors are sterilized and sealed, the detailed functions of reactors are difficult to analyze. Nieuwoudt et al. are the first to report overcoming this obstacle in a noninvasive manner. Cell-seeded bioreactors without perfluorocarbon were more glycolytic than those with perfluorocarbon. The system is attractive for studying in situ O_2-dependent bioreactor metabolism [29].

Imanishi et al. of the Osaka University Graduate School of Medicine conducted cell transplantation therapy using synovial membrane-derived mesenchymal stem cells (SM MSCs). They transplanted 5×10^6 SM MSCs to the rat myocardial infarction model and proved that the cells improved cardiac performance significantly. They also pointed out the possibility of the transdifferentiation of engrafted cells into a myogenic lineage that inhibits myocardial fibrosis. Recently, the differences in the MSCs derived from different tissues such as bone marrow, adipose tissue, fetal membrane, or synovial membrane, have been widely studied and discussed. Although details are still unclear, such information is very important for successful autologous cell transplantation therapy both in preclinical and in clinical studies [30].

One of the most important issues in tissue engineering is quality control of the sample. Oie et al. from the National Cardiovascular Center Research Institute developed a tactile mapping system (TMS), which enabled easy observation of the distribution of the elastic modulus over a tissue-slice sample. They demonstrated the feasibility of TMS application in elasticity mapping of native tissues at the extracellular matrix level. By adjusting the tip diameter of the sensor probe to the size of the microstructure of the tissue, it was possible to easily adjust the space resolution and the indentation depth and to significantly reduce the measuring time. They concluded that TMS will prove to be a powerful tool for successful in vivo tissue fabrication and precise evaluation of the degree of tissue maturation after implantation [31].

A new idea in tissue-engineered blood vessels was proposed by Nam et al. from Tokyo Medical and Dental University, who attempted to chemically crosslink decellularized blood vessel tissue and to perform crosslinking with a polymer in order to control its stability and functionality. For this purpose, they crosslinked tissue by intrahelical, interhelical, and intermolecular crosslinking between the polymer and the collagen helix. The tissue intermolecularly crosslinked with polymer showed the highest stability against heat and degradation caused by collagenase. The mechanical strength test showed that the Young's moduli were different for the intra-/interhelically and intermolecularly crosslinked tissues, with the latter being stiffer. They concluded that by crosslinking the tissue with polymer, it is possible to provide the tissue with

antithrombogenic and anticalcification properties. Thrombosis and calcification have been problems in the clinical application of engineered tissues [32].

Culture conditions are important factors for tissue engineering. Conventional methods for differentiation of chondroprogenitor cells on plastic plates have been reported to face several problems that hinder the application of this method for the treatment of chondrogenic injury. Atashi et al. from Tarbiat Modares University, Iran, reported the effect of poly-L-lysine (PLL)-coated plastic surfaces and fetal calf serum concentration on the chondroprogenitor cells. Histochemical analysis and toluidine blue staining showed that cartilaginous proteoglycans accumulated in aggregated cells. According to the results, PLL-coated plates seem to be an advantageous extracellular matrix choice for the preparation of aggregates for chondrogenesis differentiation. Atashi et al. concluded that PLL may have some effect on the adhesive properties of chondroprogenitor cells and may be useful for cartilage engineering [33].

Dialysis

On the topic of dialysis, we published two original articles in 2009.

Tomisawa and Yamashita revealed that the strong adsorption characteristics for low molecular weight proteins in PMMA showed good agreement as they established that the clearances for cytokines in clinical PMMA-CHDF were dependent on concentration. They also revealed the differences in the adsorption mechanism between PMMA and PEPA membranes. The former may be due mainly to occlusion of the pores and the latter to hydrophobic interaction. They mentioned that the amount of adsorbed albumin loss by the dialysis membrane should be taken into account in discussions of the clinical criterion of albumin loss [34].

Petrović and Stojimirović reported on the possible predictive value of cardiac troponins (cTnT and cTnI) on the outcome in 115 hemodialysis (HD) patients over a 2-year follow-up period. They revealed that serum cTnT concentration was increased in 37.39% of patients and elevated serum cTnI concentration in 11.3% of HD patients without acute coronary syndrome symptoms or signs. They also reported that patients with serum cTnT levels greater than 0.10 ng/ml had significantly lower overall and cardiovascular survival rates than patients with less than 0.10 ng/ml and that patients with serum cTnI levels greater than 0.15 ng/ml had significantly lower overall and cardiovascular survival rates than patients with less than 0.15 ng/ml. They concluded that cTn levels are significant outcome predictors in regular HD patients [35].

Artificial liver and pancreas

With regard to artificial liver and pancreas, we published one review paper and two original articles in 2009.

Hoshino et al. of Shisei Hospital, reviewed recent progress in mechanical artificial pancreas (MAP). In this review, MAP is composed of three major components: a blood glucose control algorithm, a drug administration system, and a glucose sensor. Although significant progress in the development of MAP has been made, its use in clinical situations or for research purposes is limited at present. The authors insisted that the main limiting factor is the slow progress in the development of glucose sensors; however, more widespread clinical application of MAP will occur in the near future, considering the number of reliable long-life intravenous glucose sensors under development [36].

Yoshimi et al. of the Shibaura Institute of Technology contributed to the development of a glucose sensor for MAP. They developed an enzyme-free glucose sensor using the gate effect of a molecularly imprinted polymer. This sensor has the advantages of improved stability and a simplified manufacturing procedure. The sensor, an electrode grafted to a glucose-imprinted polymer (methylene bisacrylamide), can detect glucose in aqueous solution through the gate effect with sufficiently high selectivity, a wide dynamic range, and fast response [37].

Okura et al. of the Osaka University Graduate School of Medicine investigated the transdifferentiation of human adipose tissue-derived stromal cells (ADSCs) into insulin-producing clusters. The important point in their method was the culturing of under-floating conditions in the final step of differentiation. Their insulin-producing cells derived from ADSCs could be potentially useful for cell therapy of type 1 diabetes mellitus [38].

Recently, the importance of strict blood glucose control and intensive insulin therapy has been elucidated in critical care medicine. Therefore, rapid progress of this field is expected.

Artificial skin, muscle, bone, and neuron

One review article, a minireview, two original and a brief communication contributions were published in the journal in 2009 on the topic of musculoskeletal systems.

A review by Date and Yasuhara summarizes clinical research in cell transplantation and regenerative therapy for the treatment of Parkinson's disease and cerebral ischemia from the first report in 1985 to the present. In their summary, various types of cells, such as chromaffin cells, nigral cells, and carotid body cells, as well as neurotrophic factors are introduced. Neural stem cells are promising

sources for dopaminergic neurons if a more suitable procedure is established in differentiation. In the treatment of cerebral ischemia, intracerebral neural transplantation, neutrophilic factor-secreting cell line grafting, and adult-derived neural stem cell grafting are mentioned [39].

Kawada and Sugimachi of the National Cardiovascular Center Research Institute reviewed the artificial neural interface for bionic cardiovascular treatment. They introduced the following significant basic technologies: first, the rule for decoding native sympathetic nerve activity into a heart rate using transfer function analysis as a framework for a neurally regulated cardiac pacemaker; second, a bionic baroreflex system to restore the baroreflex buffering function using electrical stimulation of the celiac ganglion in a rat model of orthostatic hypotension; third, the implantation of a neural interface into the right vagal nerve, demonstrating that intermittent vagal stimulation significantly improved the survival rate in rats with chronic heart failure following myocardial infarction. Although several practical problems need to be resolved, such as those related to the development of electrodes feasible for long-term nerve activity recording, studies of artificial neural interfaces with the autonomic nervous system have great possibilities in the field of cardiovascular treatment [40].

To develop a bio-actuator using tissue-engineered muscle, control of the contractility by an exogenous signal such as electrical pulse stimulation is essential. Yamasaki et al. cultured C2C12 myoblasts and differentiated them into myotubes using a differentiation medium containing horse serum. They found that the myotubes contracted synchronously with electrical pulse and depended on the pulse frequency. In addition, tissue-engineered skeletal muscle made from C2C12 cells embedded in type-I collagen gel, approximately 13.5 mm in length, showed similar contractile performance and the contraction was visible with the naked eye. They concluded that a bio-actuator could be developed and controlled using electrical pulses [41].

Choi and colleagues from The University of Tokyo reported a new tailor-made artificial bone implant with both horizontal and vertical cylindrical holes 2 mm in diameter prefabricated from α-tricalcium phosphate (α-TCP) powder using an ink-jet printer. The implants, 15 mm × 15 mm, were implanted into bone defects created in dog skulls and tested for bone defect repair ability. Computed tomography and histological examination revealed that the new implants showed better defect repair compared with sintered hydroxyapatite bone substitute. However, when compared with their previous results of similar implants without vertical holes, the amount of regenerated bone was even less, suggesting that the addition of vertical holes had no advantage [42].

Saijo et al. from The University of Tokyo reported a series of clinical applications of artificial bone implants made from α-TCP using ink-jet printing technology. Ten patients with maxillofacial deformities were implanted with computer-aided dimensionally fabricated artificial bones according to the shape of the bone defect determined in simulation surgery using a plaster model. The implants showed dimensional compatibility, leading to reduced operation time and hemorrhage, partial integration to host bone, and satisfactory esthetic results in all patients, without serious complications. Their technologies merit much attention and further investigation [43].

Others

In 2009, we had four articles in the category of "Others": one original article, two reviews, and one minireview.

Ifukube introduced some basic unresolved issues and potential solutions in the development of artificial sensory organs, such as cochlear implants, brainstem implants, artificial vision, and artificial retinas. Surprisingly, with advanced cochlear implants, 50000 hearing-impaired patients have regained hearing, accompanied by activation of the speech area in the brain. We would expect the same success for artificial retinas although it is not known whether the plasticity of the brain can function as well as has been shown with the cochlear implants [44].

Currently, no treatment can restore vision to patients with retinitis pigmentosa once they have lost their sight. Sakaguchi et al. of the Osaka University Medical School evaluated the safety and efficacy of artificial vision by using a direct optic nerve electrode in a blind patient with retinitis pigmentosa. They implanted the device, comprising three wire electrodes (0.05 mm in diameter), into the optic disk of the patient. They reported that no complication occurred intraoperatively or during the follow-up period, and that the wires remained functionally stable for at least 6 months of follow-up. They reported that localized visual sensations were produced in a blind patient with advanced retinitis pigmentosa 6 months after implantation of the visual prosthesis system [45].

Advances in devices and techniques continue in the field of medicine. However, unpredictable problems such as device failure and other adverse events sometimes occur.

Tateishi and Tomizawa of the Department of Cardiovascular Surgery, Tokyo Women's Medical University, reviewed the literature on unretrieved medical device fragments, and summarized causes, complications, methods, and indications of retrieval. They reviewed the causes of intravascular foreign bodies in terms of three categories: inappropriate techniques and procedures, device defects, and patient factors. They concluded that use of a device

tracking system, a reporting system of adverse events, and patient information is recommended to promote patient safety as a first priority [46].

Biomechanics is one of the backbones in research on artificial organs. Nishida of the National Institute of Advanced Industrial Science and Technology reviewed research achievements in the field of biomechanics that have been attained in the past few years. Recent advances in certain biomechanics subfields continue to extend the frontier of those studies that seek to understand the most basic life phenomena as well as application studies into advanced medical techniques. He summarized recent achievements in the following subfields of biomechanics: computational biomechanics, circulatory biomechanics, cell biomechanics, muscle and skeletal biomechanics, biomechanics of the motion of bodies and living things, impact biomechanics, and biomechanics in artificial organ studies [47].

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人工肺の研究開発・臨床応用

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1. はじめに

「人工肺」は、生体肺の呼吸機能、すなわち血液に酸素を添加し血液から炭酸ガスを除去するガス交換の働きを肩代わりする装置で、主として心臓手術（開心術）時の「人工心肺装置」の一部として用いられる。人工心肺装置を用いた体外循環は、1953年に初めて臨床応用されて以来開心術の普及とともに発展を遂げ、今日の開心術における最も基本的な技術となっている。この間人工肺は、多孔質中空糸ガス交換膜の開発などによって性能が向上し、現在では開心術用の使用においてはかなり満足できるガス交換性能を獲得した感がある。その一方で、全身ヘパリン化のもとで行われる開心術においても、血液接触面での血液反応の抑制やヘパリン投与量削減による出血量低減を期待して、血液適合化処理を施した人工肺や人工心肺回路の使用が試みられており、またECMO（Extracorporeal Membrane Oxygenation）やPCPS（Percutaneous Cardiopulmonary Support）など補助循環への応用を目的とした研究開発・臨床応用も進められている。

このように人工心肺装置や補助循環装置として用いられる人工肺に対しては、ガス交換性能のみならず、耐久性や血液適合性、操作性・安全性、熱交換性能などが求められる。また、具体的設計においては、ガス交換部のみならず、熱交換部、貯血槽や除泡部、ポートや血流分配構造、ケーシングやホールダーなど、周辺部分も含めた様々な材料的・構造的ノウハウが集積されている。本稿では、人工肺の研究開発と臨床応用について、その現況を中心に概説する。

2. 開心術と人工心肺装置

日本では毎年3万例以上、米国では毎年10万例以上の開心術が行われている。通常の開心術では、実際に心臓自体に手を加えている時間は2～3時間以内であり、術後はほとんどの患者さんが元気に退院・社会復帰している。開心術の病院死亡率は一般的な待機手術では1%以下、緊急手術や重症例を含めても3～4%程度であり、今日の開心術は広く定着した日常的な医療であると言える。開心術を安全に行う上での最大の契機となったのが人工心肺装置の登場である。人工心肺装置が生体の心臓と肺の機能を肩代わりすることで、心臓内部を血液が殆ど流れない状態にしたり、心臓の動きを一旦停止させることが可能となり、これによって開心術が今日のように短時間で安全に行えるようになった。

人工心肺装置（図1）は、全身から血液が還ってくる大静脈と心臓が全身にむけて血液を送り出す大動脈の間で並列に患者と接続され、血液が生体の心臓と肺をバイパスする形で装置内を灌流することで体外循環が成立する。人工心

著者プロフィール
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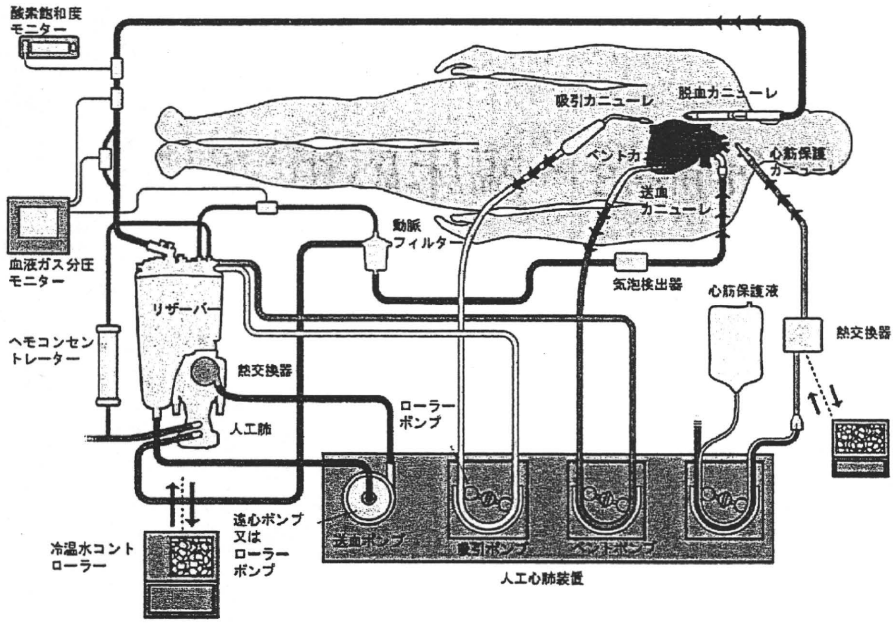

図1　人工心肺装置

肺装置は、大静脈に留置した脱血管を通して血液を装置に流れ込ませる脱血ライン、術野に貯まった血液を回収する吸引ライン、脱血した血液や吸引血を一時的に貯める貯血槽、ガス交換を行う人工肺、ガス交換後の血液を送血するための血液ポンプ、送血血液中の微小気泡や微小凝血塊を取り除く動脈フィルター、動脈に留置した送血管まで血液を導く送血ラインなどで構成される。そして、これらの構成パーツの中でも中心的な役割を果たしているのが、ガス交換機能を担う人工肺である。

3. 人工肺開発の歴史

人工肺開発の歴史を辿ると、18世紀の終わりには生理学の研究を目的として人工的にガス交換を行う装置が作製されたが、これは身体の呼吸機能を代行するためのものではなかった。実際の患者治療に使用するための装置としては、米国Massachusetts General hospitalで外科医のGibbonが、救命できなかったある患者の臨床経験をきっかけとして独自で研究を進め、1937年に世界で初めて動物の呼吸と循環を代行する実験に成功したことに遡る。その後IBM社の協力を得て、金網の平板を並列させた「スクリーン型」という人工肺を完成させ、20年間におよぶ研究を経て、1953年にMayo Clinicにおいて心房中隔欠損症患者の開心術として最初の臨床応用が行われた[1)]。我が国においても、1956年には曲直部[2)]が本邦で初めての人工心肺使用下での開心術成功例を報告した。Gibbonの「スクリーン型」人工肺は「フィルム型」人工肺へと進化し、さらにCross, Kayによって高性能・高耐久性を有する回転円板型人工肺（図2）が開発され[3)]、1960年台に広く普及した。これらのタイプは何れも、金属表面に静脈脱血した血液の薄膜を形成して吹送する酸素ガスとの間でガス交換を行うという機構であった。

その後、大量生産・ディスポーザブル化が可能な気泡型人工肺が出現し、1970年代を代表する人工肺となった。これは、血液と酸素ガスを直接混ぜ合わせて十分にガス交換を行った後に、血液中の気泡を取り除いて全身に返すという機構のものである。ただ、この気泡型人工肺は、

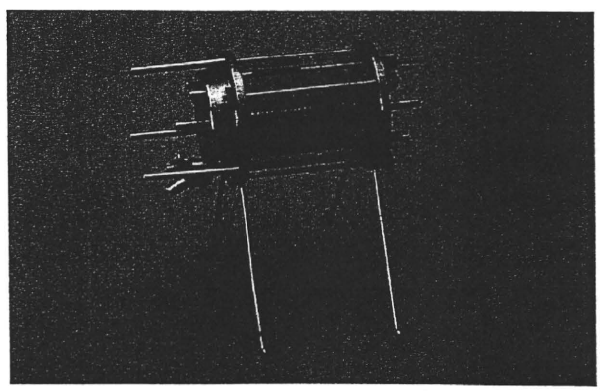

図2　開発初期の回転円板型人工肺（Pempco Kay-Cross型,1956年）

ガス交換効率は非常に良好であったが、その一方で血液が大量の酸素ガスと直接接触するために、微小気泡の残存や血液損傷、さらに血液の凝固反応や炎症反応が著しく亢進するという短所があった。

一方、1944年にKolffが、透析患者の血液が人工腎のセロファン膜を介して酸素加される現象に気付いて人工肺への応用を試みたものが、現在主に用いられている「膜型人工肺」の開発の端緒である[4]。血液と酸素が直接接触しない膜型人工肺は「生理的人工肺」として期待されたが、技術的困難も多く、1968年になってようやくシリコンラバー膜を用いたものが実用化された。これをコイル状に巻いた人工肺はKolobow肺として発展し、耐久性に優れていることからECMOとしての応用が提案・研究されるようになった[5]。しかし、当初は気泡型と比べてガス交換性能が劣り、また気泡除去が難しく操作が煩雑で、さらにコストダウンが困難であるなど、まだまだ多くの問題を抱えていた。

膜型人工肺の革新技術となったのが、1979年に我が国の研究グループによって開発された「多孔質中空糸膜」である[6]。サブミクロンの微小孔を有する高分子膜を用いた多孔質中空糸膜型人工肺では、材料の疎水性によって血液は微小孔から漏れ出ない(ただし長期間の使用では、蛋白吸着・疎水性低下によって血漿成分がガス相に漏れ出す「血漿漏出」が起こる)。この人工肺は、従来のシリコンラバー膜型肺と気泡型肺の利点を併せ持つ人工肺として、またたく間に汎用人工肺としての地位を確立した。

4. 現在の膜型人工肺の基本構造

現在用いられている人工肺は、上述の「気泡型」と「膜型」の2種類であり、我が国や米国などでは後者がほぼ100%を占める。膜型人工肺に用いられるガス交換膜としては、シリコンラバー製の均質膜およびポリプロピレン製を中心とする多孔質膜があり、特殊な多孔質膜として薄い均質層をもつ非対称膜がある(図3)。シリコンラバー膜の膜厚は100 μm程度で、血液と酸素ガスは直接接触せず、膜を介する拡散によってガス交換が行われる。一方、多孔質膜の膜厚は20～30 μmで、孔径0.03～0.07 μmの多数の微小孔が膜を貫通して内外面で開口し、血液接触面において微小な血液/ガス界面を形成してガス交換が行われる。

膜モジュールの形態としては平膜と中空糸膜があるが、シリコンラバー膜のKolobow肺を除いて、現在はほぼ全て中空糸膜である。直径200～300 μmの中空糸膜は、それ自体が支持組織となるため設計の自由度も高く、体積当たりのガス交換膜面積が多く、人工肺内部の血流状態の制御性も良好であるなど、多くの利点を有している。開発当初は中空糸の内側を血液が流れる「内部灌流方式」であったが、現在は中空糸の外側を血液が流れる「外部灌流方式」が主流となっている。外部灌流方式の方が人工肺内部の圧損失が低く、また設計の工夫によってより効率的なガス交換性能が得られるからである。

中空糸は束ねたり編んだりしてバンドル化されて、人工肺のケーシングに収容される(図4)。バンドルの両端はポッティング剤という接着剤

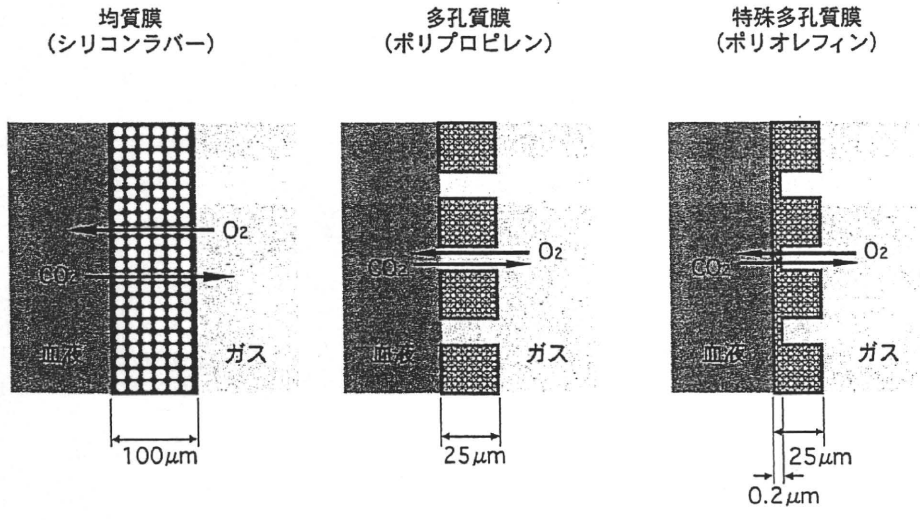

図3　膜型人工肺に用いられるガス交換膜の種類

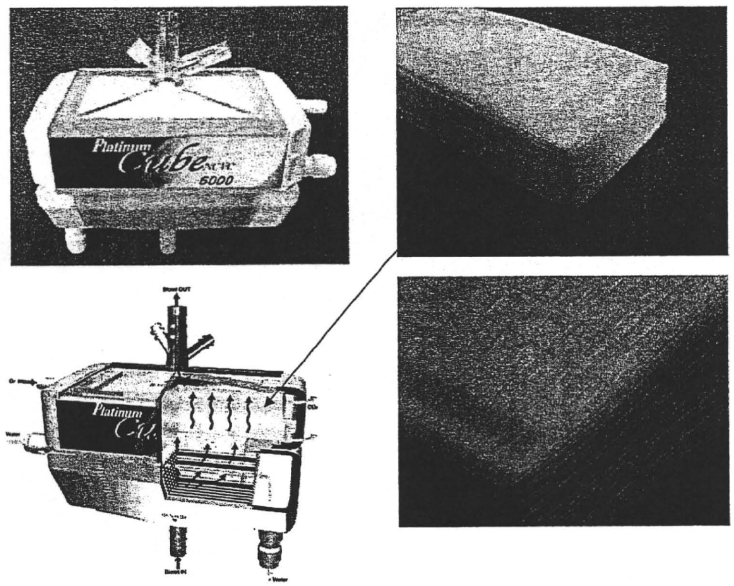

図４　ガス交換膜（中空糸バンドル）を内蔵した膜型人工肺

で固められる。バンドル化に際しては、内部の血流状態を最適化することが重要であり、中空糸をできるだけ均等な間隔で、しかも適当な密度（充填率）で配置する必要がある。中空糸間の距離が不均一だと流れにチャンネリングが生じてガス交換効率は低下し、逆に密に束ね過ぎると圧力損失が大きくなって血球破壊や血液の鬱滞を招く。血液が効率的に混ざり合うような血流状態の確保も重要であり、これらの要因を勘案した最適な充填率は、経験的に40～45%程度とされている。

現在の人工肺は、熱交換器を内蔵するものが一般的である。熱交換器には金属管（直径2 mm前後のステンレス管を複数用いた多管式やベローズ型など）を用いるものが多いが、最近はポリマー製のものも使用されるようになってきている。毎分10L以上の温冷水を灌流して冷却・復温を行うために耐久性が求められ、また血流抵抗をあまり増加させることなく熱交換効率を向上させるための流路や形状の最適化に工夫がなされている。

プレコネクトによる操作性の向上を考慮して、貯血槽や除泡部を人工肺本体と一体化させた製品も多い。さらに近年では、動脈血フィルターを内蔵した人工肺がテルモ社から「CAPIOX FX」として製品化されており、プレコネクト化を発展させて回路チューブの一部を廃することにより、血液充填量の減少や圧力損失の低減効

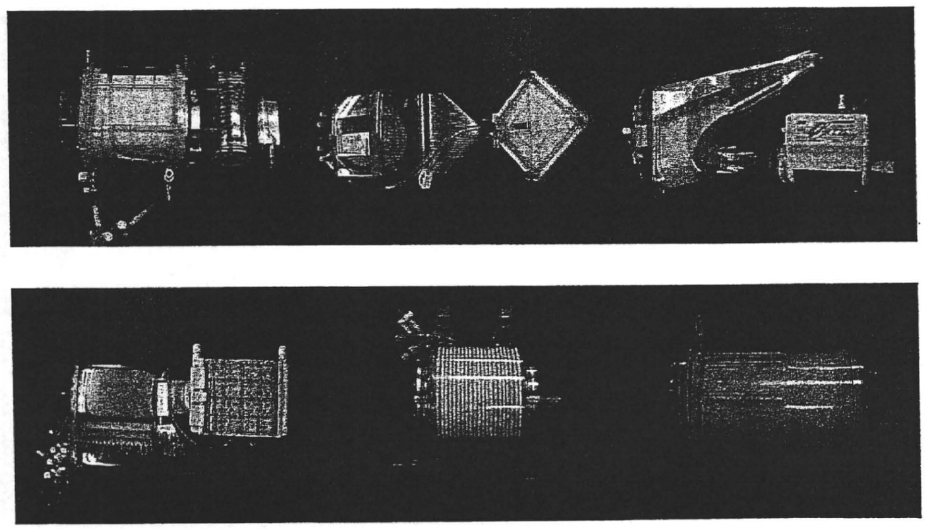

図５　最近の外部灌流方式中空糸膜型人工肺の製品例

果が期待されている。最近の外部灌流方式中空糸膜型人工肺の製品例を図5に示す。

5. 人工肺の臨床使用の現状と動向

我が国における最近の人工肺の使用状況については、矢野経済研究所が行っている出荷数ベースの調査[7]によると、2008年度の総出荷数は44,238個で、このうち一般開心術用が39,418個、経皮的心肺補助(PCPS)や呼吸補助(ECMO)など補助循環用が4,820個となっている。開心術用人工肺の使用数は、2003年頃までは毎年1,000～2,000個前後のコンスタントな増加（年間増加率3～6%）を示してきたが、以後は明らかな頭打ち傾向を示している。これには、冠動脈ステントなどの経皮的冠動脈インターベンション(PCI)の普及、そして体外循環を使わない冠動脈バイパス術（off-pump CABG）症例の増加などが大きく影響しているものと考えられる[8]。また、CABG症例数が2003年の22,188例をピークに漸減傾向を示す中で、off-pump症例数も2004年の12,018例をピークに減少傾向にあることから、2005年以降の虚血性心疾患に対するDrug Eluting Stent (DES)症例数の増加がこれらの傾向に大きく影響を及ぼしているものと推察される。

一方、補助循環症例への使用数も2002年頃までは毎年10～20%前後の顕著な増加を示してきたが、最近は増加傾向が鈍りつつある。膜型人工肺研究会が毎年行っているアンケート調査によると、2007年のECMOの施行症例数は、回答のあった75施設の合計で465例となっている[9]。また、PCPS研究会が行った全国集計調査（回答施設148施設）では、PCPS症例数は年間700～800例に達し、臨床成績も明らかに向上してきている[10]。日本胸部外科学会による補助循環の統計[11]では、2007年の人工肺を用いた心肺補助症例数は1,356例となっているが、循環器内科領域や救命救急、集中治療領域での使用数は集計に入っていないため、実際の症例数はこの数倍に上るものと考えられる。

世界的な集計としては、米国ミシガン大学を拠点とするExtracorporeal Life Support Organization（ELSO）が毎年全世界の主要なECMOセンターにおける症例の登録・解析を行っている。2008年6月の報告[12]によると、調査が開始された1987年以降の累積症例数は37,717例に達し、離脱率は75%、生存率は63%となっている。123施設から回答を得た2007年の症例数は2,290例に上っており、現在も増加傾向にある。

6. 人工肺の高機能化を目指した研究開発の動向

(1) 血漿漏出の防止

人工肺は、現在では開心術用の使用においてはほぼ十分なガス交換性能を有するに至ったと言える。その一方で、ECMOやPCPS等の補助循環への応用が進むとともに、さらなる小型化や、長期耐久性、高い抗血栓性などが求められるようになり、ガス交換膜材質の開発・改良や回路への抗血栓性付与などに重点をおいた研究開発が続けられている。

通常のポリプロピレン製多孔質膜では、長期間使用時に疎水性が失われて微小孔からの血漿漏出を生じるため、数日程度の使用が限界である。また、血液-ガス界面を有するために、微小気泡の混入や生体の炎症反応・血液凝固反応を亢進させる。テルモ社では相分離方式を用いた独自の製膜技術によって、微小孔径の均一化による耐久性向上を図ったポリプロピレン製多孔質膜を開発し、製品に用いている。血液-ガス直接接触の問題を克服するガス交換膜としては、種々の複合膜が検討されている。シリコンやシリカの微小孔への充填、血液接触面へのフッ素コーティングなど、ガス交換性能を可及的維持し得る材料で多孔質膜の微小孔を封じる試みが行われ、シリコンで表面コーティングを施した多孔質膜は既に実用化されている[13]。また、単一素材のガス交換膜として、シリコン中空糸膜[14]や含フッ素ポリイミド中空糸膜[15]などが開発されており、今後の製品化が期待される。

血漿漏出を防止して長期耐久性を得る上で、現在最も広く用いられているのがポリ（4-メチルペンテン-1）製の非対称膜（PMP膜）である（図6）。世界的にはMembrana GmbH社製のPMP膜がよく知られているが、膜技術の進歩を

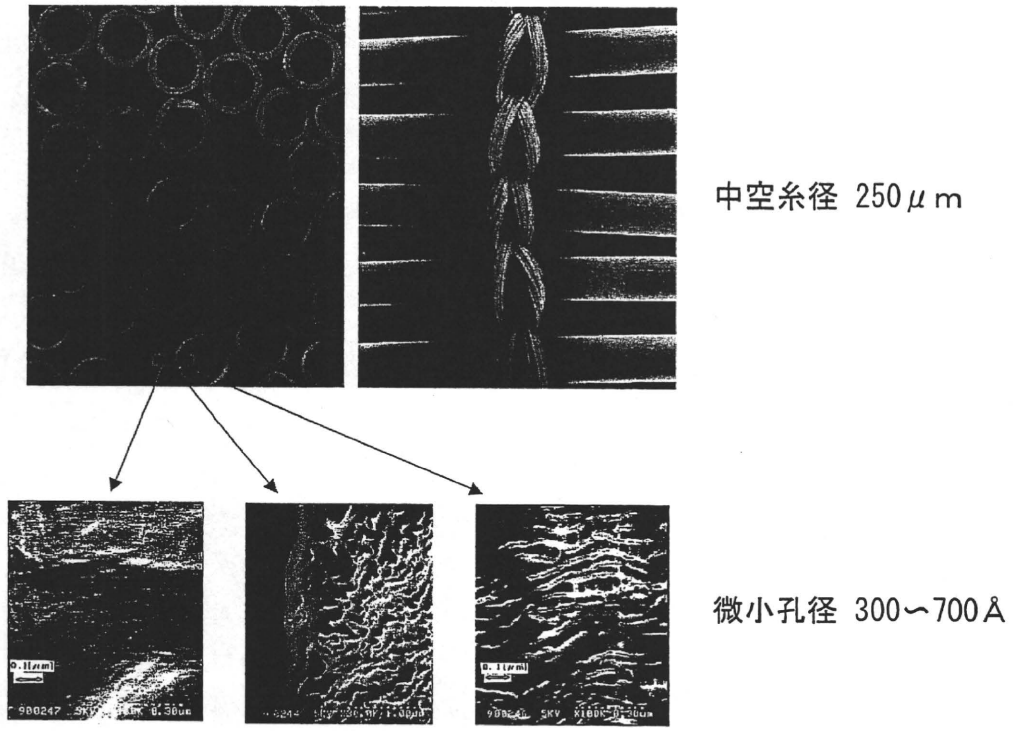

図６　ポリ（4-メチルペンテン-1）製の非対称ガス交換膜

背景に、元々半導体製造やスーパーカミオカンデで用いる超純水を作成するために開発使用されていたこのPMP製物質交換膜を人工肺に応用したのは、クラレ／大日本インキ／国立循環器病研究センターのグループによるものが最初である。1991年に世界で初めて「Menox」人工肺として製品化され[16]、その後中空糸径を細径化したガス交換膜[17]を用いた人工肺が1998年「Menox-α」として、さらに改良を加えてガス透過性を向上させた中空糸を用いた人工肺が2001年に「α-Cube」として順次製品化された。PMP膜では、多孔質膜の血液接触面に極薄の緻密層を形成して血液相とガス相を遮断することで血漿漏出を防止しているが、このような微小構造は耐久性のみならず血液適合性の面からも大きな利点である。

(2)　抗血栓性の向上

現行の人工肺は抗血栓性に乏しく、使用に際して生体由来抗凝血薬であるヘパリンを患者に投与する必要がある。開心術等の短時間使用であれば問題は少ないが、補助循環等の長期使用においては、出血傾向を惹起してリスクが増大する。ヘパリン投与量の低減を目的として人工肺に抗血栓性を付与するための様々な試みが行われてきたが、現在主に用いられているのは、血液接触面に化学的にヘパリンを導入（徐放または固定化）する方法である。とくにヘパリンを共有結合によって回路表面に固定化する技術は長期の抗血栓性が期待され、テルモ社の「Hepaface」やメドトロニック社の「Carmeda Bioactive Surface」などが既に実用化されている。

このようなヘパリン化処理を行った人工心肺回路の使用報告では、短時間の使用においては凝固系・血小板系の活性化抑制効果などが示されているが[18]、出血量抑制や手術成績などではあまり顕著な効果は示されていない。ECMOやPCPSなどでは血液適合性に加え耐久性向上における有効性も指摘されているが[19]、抗凝血薬の投与量減量は可能ながら抗凝血療法は未だに必須であり、これをほぼ不要化するためにはより強力な抗血栓性の獲得が必要である。

国立循環器病研究センターでは、東洋紡社との共同研究で、強力な抗血栓性と長期間の効力を有し、処理工程も簡単かつ低コストの優れたヘパリンコーティング「T-NCVCコーティング」の開発に成功した[20]。上述のPMP膜を用いてT-NCVCコーティングを施した人工肺は、2001