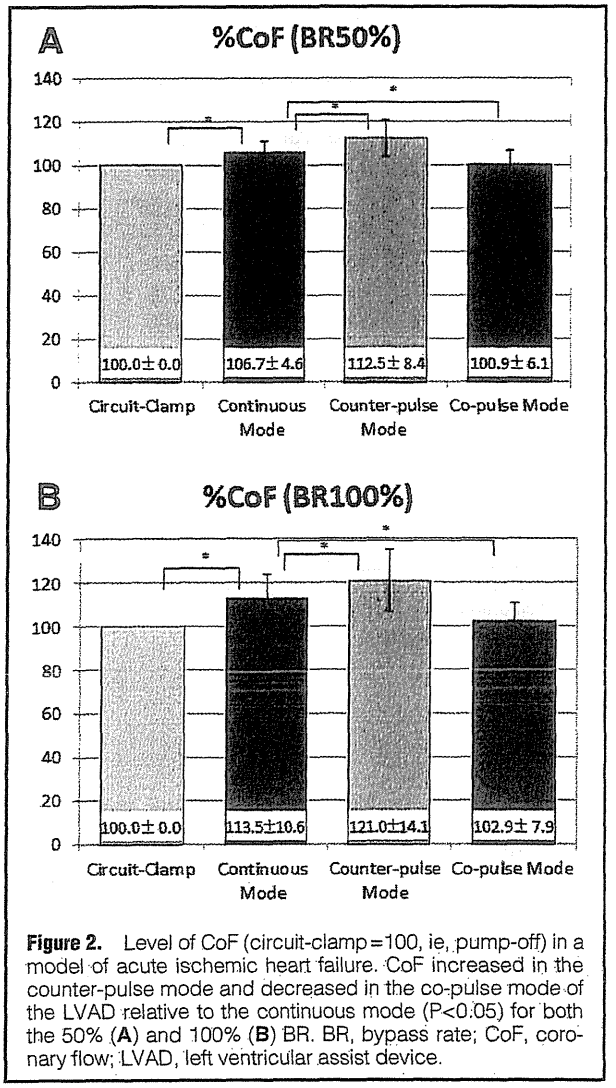

Figure 2. Level of CoF (circuit-clamp=100, ie, pump-off) in a model of acute ischemic heart failure. CoF increased in the counter-pulse mode and decreased in the co-pulse mode of the LVAD relative to the continuous mode ($P<0.05$) for both the 50% (**A**) and 100% (**B**) BR. BR, bypass rate; CoF, coronary flow; LVAD, left ventricular assist device.

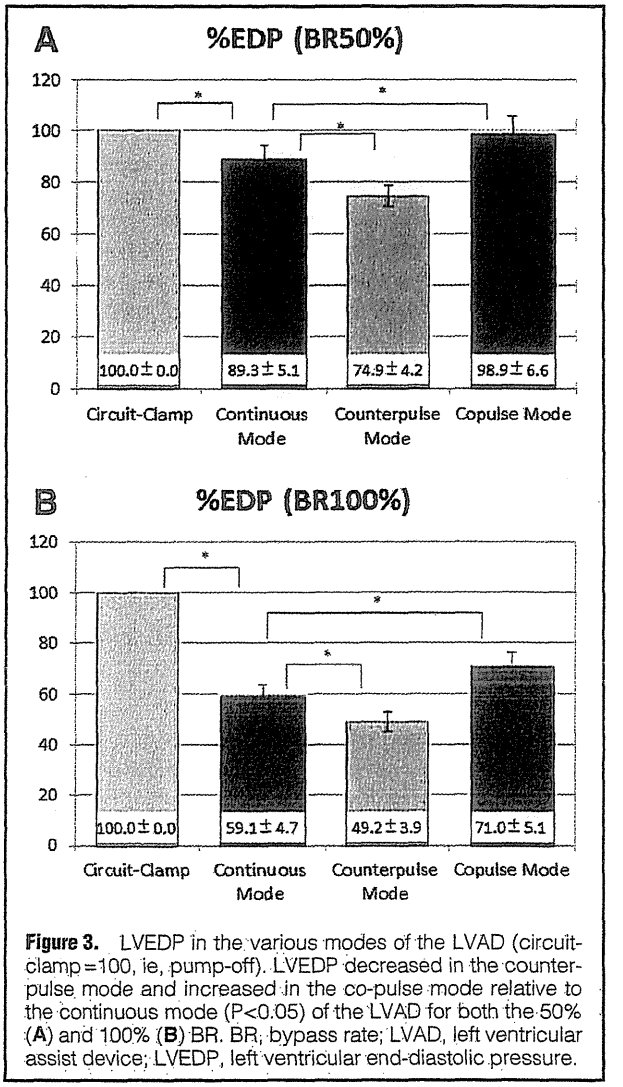

Figure 3. LVEDP in the various modes of the LVAD (circuit-clamp=100, ie, pump-off). LVEDP decreased in the counter-pulse mode and increased in the co-pulse mode relative to the continuous mode ($P<0.05$) of the LVAD for both the 50% (**A**) and 100% (**B**) BR. BR, bypass rate; LVAD, left ventricular assist device; LVEDP, left ventricular end-diastolic pressure.

time. Many reports have compared the clinical outcomes or effects on the circulatory dynamics between pulsatile and cf-LVADs.[8–29] Tatsumi's group confirmed that the change in sympathetic nervous system activity, as indicated by changes in norepinephrine levels, was higher in the non-pulsatile mode than in the pulsatile mode.[12,13] They also suggested that the high norepinephrine level in the non-pulsatile circulation would affect oxygen metabolism and worsen systemic oxygen uptake in the acute phase.[14,15] From the standpoint of hemodynamic change, Undar et al showed that pulsatile flow generated higher energy, which may be beneficial for vital organ perfusion,[16] depending on the timing of mechanical beating.[17,18] Pulsatile flow may be beneficial for end-organ microcirculation[19] and CoF,[20] but it does not change liver circulation.[21] The effect on brain metabolism also remains controversial.[22–24] The vascular system is thought to be affected by pulsatility, because it is always exposed to changes in AoP, blood flow, and growth factors.[25] Nishimura et al[26–29] reported that long-term non pulsatile LVAD caused marked structural changes in the aortic wall, and atrophic changes in aortic smooth muscle cells. They also reported that the systemic vascular resistance response to norepinephrine decreased markedly with non-pulsatile flow. The effect of long-term support with cf-LVAD remains unknown or is not considered beneficial. Among the clinical outcomes, unfavorable results with pulsatile LVAD have been reported,[8] but this may stem from the higher risks of complication with pulsatile LVAD. Because we consider that the merit of its ability to provide physiological circulation should not be completely excluded, we developed our novel driving system, the NHLCS, for the cf-LVAD.

Needless to say, CoF is considered the most important factor in determining the native heart's condition. To avoid myocardial ischemia, it is important to maintain appropriate CoF. Therefore, we considered CoF carefully when evaluating our new system. Apparently, LVADs may increase CoF by their ability to raise aortic perfusion and decrease LVEDP. Thus, many researchers have discussed the effect of LVADs on myocardial perfusion, but it remains incompletely understood.[43–47] A counter-pulse effect may be useful for increasing coronary perfusion with increasing aortic pressure in the diastolic phase.[44,48–50]

Therefore, in the present study we focused on CoF, which we expected to control with the cf-LVAD using the pulsatile driving technique. First, we noted that CoF increased in the

continuous support and counter-pulse modes in our model of acute ischemic HF. In models of the normal heart, CoF decreased and coronary artery resistance increased,[30,31] which we initially thought may have been attributable either to mechanical collapse of the coronary vascular bed with pump support or to increased vascular tone through the autoregulatory system. However, if the coronary vascular bed always collapses with LVAD, then the LVAD should also decrease CoF in models of acute HF. So the hypothesis that the LVAD may induce collapse of the coronary vascular bed is contradictory. The autoregulatory system, which changes coronary artery resistance according to the demands of myocardial perfusion, may be more accountable for these results.[51] If the LVAD creates excessive CoF, which is the situation in the normal heart, coronary artery resistance may increase and lead to a decrease in CoF at last. If the native heart in acute failure needs more myocardial perfusion, resistance may be decreased and CoF increased.

If we shift our frame of reference to the change in CoF according to the driving mode, we find that CoF always increased in the counter-pulse mode and decreased in the co-pulse mode, regardless of the heart's condition. In the counter-pulse mode, the reduction in LVEDP[52] and diastolic flow support may lead to increased CoF as the difference between aortic pressure and the internal pressure of the cardiac muscle increases. When compared with intraaortic balloon pumping (IABP), the counter-pulse mode of the NHLCS has a more active effect on reducing LVEDP, so it may be considered to be more effective for enhancing CoF.[44,48] On the other hand, in the co-pulse mode, CoF was reduced for the opposite reason. In fact, we have proved that LVEDP is reduced in the counter-pulse mode and enhanced in the co-pulse mode. We also observed a change in aortic pressure in the diastolic phase according to the driving mode. From the standpoint of coronary vascular resistance, the change in LVEDP with the driving mode also affects the resistance by wall tension. It is possible that metabolic, neurologic, or some other factors are responsible for the change in resistance. Further examination to elucidate the change in coronary vascular resistance and the determinant factors affecting it is in progress.

We have at least proved the possibility of changing the native heart load from the aspect of CoF with bypass rates of 50% and 100%. This means that we freely can produce a desirable CoF for native heart conditions by choosing the driving mode of the cf-LVAD. A bypass rate of 100% simulates a patient with acute HF needing full support. Excessive CoF may be beneficial in that situation and the counter-pulse mode with 100% bypass may be suitable. On the other hand, a bypass rate of 50% simulates weaning from the LVAD in the recovery stage. We can reduce the bypass rate for the purpose of both evaluating native heart function and training the native heart. If we can increase the strain to the native heart with the co-pulse mode (ie, no enhancement of CoF by the LVAD), it may be useful for training or for confirming the possibility of weaning from the LVAD.

We have shown the possibility of changing the CoF by a cf-LVAD using a pulsatile driving technique, but it remains unknown whether the oxygen in the coronary perfusion was used effectively. Further examination is in progress, including an analysis of myocardial oxygen consumption and the LV pressure–volume curve. Furthermore, we are now attempting to show the same result with the CoF using models of chronic HF.

Conclusions

Our experiment on goats with acute ischemic HF have revealed that the LVAD was able to change the level of CoF. Flow was higher with the counter-pulse mode and lower with the co-pulse mode, relative to the continuous support mode, which usually applies to clinical use. This result means that we can change the CoF by controlling the LVAD's rotation in synchrony with the heartbeat. With the ability to freely change CoF by cf-LVAD using our NHLCS, establishing a BTR may have a better prognosis, especially for patients with HF of ischemic etiology.

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REVIEW

Journal of Artificial Organs 2012: the year in review

Journal of Artificial Organs Editorial Committee

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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 practical development and clinical applications. The JAO, an international journal with articles published in English, is the official journal of the Japanese Society for Artificial Organs (JSAO). We believe that JAO has a very high potential for promoting interest in the field of artificial organs not only in Japan but also in other parts of the world. We are also convinced that the specialization, originality, and level of science of this journal are at the highest in the field. The impact factor announced in the *Journal Citation Reports* for 2011 was 1.593, demonstrating a slight increase from 1.488 in the previous year. We are very proud of this impact factor, which will certainly enhance international interest in the journal. Actually, the number of papers submitted to JAO has been drastically increasing during the last several years after obtaining the impact factor.

From the beginning with Volume 1 in 1998 to the last issue (Volume 15) in 2012, we have received submissions from 25 countries in the world, and we have accepted a

Y. Sawa
Division of Cardiovascular Surgery, Department of Surgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
e-mail: sawa@surg1.med.osaka-u.ac.jp

E. Tatsumi · T. Tsukiya
Department of Artificial Organs, National Cerebral and Cardiovascular Center Research Institute, Suita, Osaka, Japan

K. Matsuda
Emergency and Critical Care Medicine, University of Yamanashi Hospital, Chuo, Japan

K. Fukunaga
Faculty of Health Sciences, Kyorin University, Hachioji, Tokyo, Japan

A. Kishida
Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, Tokyo, Japan

T. Masuzawa
Department of Mechanical Engineering, Ibaraki University, Hitachi, Japan

G. Matsumiya
Department of Cardiovascular Surgery, Chiba University Graduate School of Medicine, Chiba, Japan

A. Myoui
Medical Center for Translational Research, Osaka University Hospital, Osaka, Japan

M. Nishimura
Division of Organ Regeneration Surgery, Tottori University Faculty of Medicine, Yonago, Japan

T. Nishimura
Department of Therapeutic Strategy for Heart Failure, The University of Tokyo, Tokyo, Japan

T. Nishinaka
Department of Cardiovascular Surgery, Tokyo Women's Medical University, Tokyo, Japan

E. Okamoto
Department of Human Science and Informatics, School of Bioscience and Engineering, Tokai University, Sapporo, Japan

total of 672 papers for publication through the peer review process. Since 2006, we have been continuing to review and summarize all the articles published in JAO in the past one year to provide an overview for our readers [1–7]. We decided to carry out this practice this year also, but at the same time we have changed our policy so that we review not all the articles but only selected papers in Volume 15. In this volume, we published 61 articles, amounting to 406 pages in total, including 35 original papers, 6 review papers, 1 minireview, 9 case reports, 5 brief communications, 1 chairperson's comment, and 4 obituaries. These papers were related to the many aspects of basic research, development, and clinical application of artificial organs, covering a variety of subfields including artificial hearts, cardiopulmonary bypass, blood vessel prosthesis, artificial valves, dialysis, apheresis, artificial pancreas, retinal prosthesis, biomaterials, tissue engineering, regeneration therapy, regulatory science, and others. The yearly acceptance rate for the four issues of Volume 15 was 69 %. For Volume 15, a total of 104 reviewers who were specialists in artificial organs and interdisciplinary fields helped our authors to improve their manuscripts through thoughtful reviews, critiques, and suggestions. We are very happy to present such excellent work in JAO.

We would like to express our profound gratitude to all authors, reviewers, and members from all over the world, and express the hope that they will continue to support our journal.

Artificial heart (basic)

Ferrari et al. [8] of the Institute of Clinical Physiology reported a modular computational model able to interact with ventricular assist devices (VAD) for research and educational application. The modular computational model consists of five functional modules (left and right ventricle, systemic circulation, pulmonary circulation, and coronary circulation). They interface a pulsatile VAD model with the modular model, and it can simulate hemodynamic waveforms in different patho-physiological conditions under VAD assistance.

Akagawa et al. [9] of the National Cerebral and Cardiovascular Center examined the influence of the port angle of the pulsatile ventricular assist device by means of a flow visualization study. They visualized flow within pumps with three different port angles (0°, 30°, 45°) by means of particle image velocimetry. The circular flow parallel to the plane of the diaphragm-housing junction changed with the port angle, and they concluded that a port angle of 0° may be suitable for their pump to obtain favorable washout effect.

Umeki et al. [10] analyzed the end-diastolic volume (EDV) to determine whether it is possible to change the native heart load by using a centrifugal LVAD which can be regulated for the rotational speed synchronized with the heart beat. They studied 5 goats with normal hearts and 5 goats with acute LV dysfunction because of microembolization of the coronary artery. Counter-pulse and copulse driving modes with the bypass rate of 100 % are produced by changing the rotational speed of the pump synchronized with the heart beat. The EDV decreased in the counter-pulse mode and increased in the co-pulse mode, compared with the continuous mode ($p < 0.05$), in both the normal and acute-heart-failure models. This result means it may be possible to achieve favorable EDV and native heart load by controlling the rotation of continuous-flow LVAD, so it is synchronized with the cardiac beat.

Kimura et al. [11] reported the hemodynamic influence of two types of valve on pump performance with the NIPRO-ventricular assist device. They underwent a periodic pump exchange in six patients from a pump with a Sorin Carbocast (SC) valve to the one with a Medtronic Hall (MH) valve. No difference was found in patients' blood pressure, serum LDH or AST levels although the pump flow tended to increase under the same drive conditions. They showed that the hemodynamic influence due to replacement of the SC valve with the MH valve in the NIPRO-VAD was insignificant.

Takaseya et al. [12] have studied the hemodynamic differences between the awake and anesthetized conditions in calves. This topic of very important for the researchers who are engaged with animal experiments in development of medical devices. The authors quantified the effect of experimental therapeutic actions on hemodynamic parameters.

Abe et al. reported the helical flow pump (HFP) for developing a total artificial heart. The HFP has a hydrodynamic levitation impeller, stator coils at the core position, and double helical-volute pump housing. A

S. Tokunaga
The Department of Cardiovascular Surgery, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan

T. Tomo
Second Department of Internal Medicine, Faculty of Medicine, Oita University, Yufu, Japan

Y. Yagi
Department of Clinical Engineering, Kyoto Prefectural University of Medicine, Kyoto, Japan

T. Yamaoka
Department of Biomedical Engineering, National Cerebral and Cardiovascular Center Research Institute, Suita, Japan

Journal of Artificial Organs Editorial Committee (✉)
Osaka, Japan
e-mail: sawa@surg1.med.osaka-u.ac.jp

hydrodynamic bearing is formed between the stator and impeller. The developed HFP showed maximum output of 19 l/min against 100 mmHg of pressure head and 11 % maximum efficiency. Hydrodynamic levitation of the impeller was possible with higher than 1,000 rpm rotation speed. The HFP was implanted in two goats with a left ventricular bypass method. No thrombus was found in the pump after 203 days of pumping in the first experiment. A white thrombus was found in the pump after 23 days of pumping in the second experiment [13].

Artificial heart (clinical)

Kainuma et al. [14] reported an end-stage heart failure patient complicated with severe renal dysfunction. Renal biopsy demonstrated no significant glomerular change and only mild tubular atrophy and interstitial fibrosis, which suggested reversibility of renal function. They implanted a Jarvik 2000 through left thoracotomy as the patient had a previous history of cardiac operation. The patient had significant recovery of renal function and became eligible for heart transplantation. Reversibility of renal function is often difficult to expect from an ordinal kidney function test. They suggested that renal biopsy is useful to clarify the etiology of renal dysfunction, although more investigation is mandatory to confirm its usefulness to determine the outcome of renal function following LVAD implantation.

Kawamura et al. [15] reported a successful case of a DuraHeart left ventricular assist device (LVAD) exchange via a subcostal approach due to the magnetic levitation system failure. The importance of positional correction of the inflow conduit was emphasised.

Morito et al. [16] of The University of Tokyo reported a successfully treated patient with a left ventricular assist device for cerebral hemorrhage using computed tomography angiography (CTA). They demonstrate the hemorrhagic source clearly with CTA, and they concluded the information gained from CTA is particularly useful in life-saving neurosurgical intervention for patients with an LVAD implant who develop cerebral hemorrhage.

Goto et al. [17] reported a change in VAD output using a mock circulatory system in a low-pressure chamber mimicking high altitude. In the Mobart system, the output decreased as the atmospheric pressure dropped, and recovered during pressurization, although the decrease was slight.

Imamura et al. [18] of The University of Tokyo reported a case complicated by right ventricular failure that manifested 3 weeks after HeartMate II implantation and her right ventricular function got progressively worse. They speculated the smaller size of the left ventricle and untreated tricuspid regurgitation contributed to the development of her right ventricular failure.

Takeda et al. [19] reported a bridge to a transplant patient with HeartWare LVAD, who underwent concomitant aortic surgery at the time of device implantation. They introduced hypothermic circulatory arrest and the patient underwent hemiarch aortic replacement and partial Valsalve aneurysm repair for multiple saccular aneurysms. There have been few reports describing complicated aortic surgery concomitant with LVAD implantation because of high operative risks. They suggested that recent advances in technology and accumulated experiences enabled surgeons to lessen mortality and morbidity even in patients requiring combined aortic surgery.

Kashiwa et al. [20] of the University of Tokyo Hospital. This research was to study the circulation pump device to aid in long-term heart transplant or bridge. Hemolysis and thrombosis is a problem in the long term assisted circulation. This study has said that with the Rotaflow centrifugal pump good results were obtained.

Yoshitake et al. [21] studied the effect of the Impella LVAD pump for the patients with acute myocardial infarction with a swine model. Mechanical circulatory support using an Impella pump have shown improvement in reducing the myocardial damage.

Imamura et al. [22] of The University of Tokyo reported three patients with stage D heart failure with revised modifier A. Two of them were rescued by extracorporeal left ventricular assist device implantation, but one died because of an electrical storm before LVAD support was available. They concluded that we should consider implantation LVAD therapy as soon as possible for those who are assigned modifier A to prevent sudden arrhythmic death.

Cardiopulmonary bypass

Hanada et al. [23] of the National Cerebral and Cardiovascular Center reported the new concept of the technique for assisting renal blood circulation on an ischemic kidney in the acute cardiorenal syndrome. The new renal-selective blood perfusion technique and the prostaglandin E1 infusion improved renal vascular resistance and glomerular function, and facilitated the production of urinary excretion of sodium and water in a goat model of acute cardiorenal syndrome. The development of techniques for assisting blood circulation of a specific organ selectively with a compact device will be a new theme in the field of the study of artificial organs.

Tomizawa et al. [24] of the Tokyo Women's Medical University. This is the first study on the application of an eye-tracking approach to the analysis of ECC operation tasks to be reported in the Japanese literature. The target is obtained by comparison with a veteran newcomer to

quantify the artificial cardiopulmonary stress perfusionist. That more experienced perfusionists be distributed widely for equipment operation was suggested.

Artificial lung

Tabesh et al. of the Institute of Physiology, RWTH Aachen University.

In this study, we evaluated six oxygenators based on geometric data in a test tube hollow fiber membrane oxygenator. As a result, the Quadrox® oxygenator is a clear choice with the most efficient design with respect to its performance during the test oxygenator [25].

Blood vessel prosthesis

Ohata et al. [26] reported the clinical performance of a Terumo-Triplex vascular graft, a new three layer graft consisting of inner and outer layers of uncoated woven Dacron and a central layer of non-biodegradable elastomeric membrane. Thirteen patients, who underwent total arch replacement using a Triplex graft had significantly less total amount of tube drainage, time to drain removal, graft dilatation ratio and inflammatory reactions as compared to the patients with other vascular grafts coated with biological material. They suggested that the Triplex graft may attenuate inflammatory reaction.

Kuwabara et al. [27] reported one year results of rat carotid arterial replacement with the small-caliber vascular grafts (0.7 mm in diameter, about 5 mm in length) made of electrospun nano-scale fibers of poly-ε-caprolactone (pCL). Twenty-nine patent grafts from among the 40 implanted grafts (patency 72.5 %) were evaluated, and then no aneurysm formation was observed. The von Willebrand factor positive cells were found at the inner surface in the early phase. Even after 72 weeks, pCL had not disappeared completely. The α-smooth muscle actin and calponin positive cells increased with time within the graft wall.

Pacemaker

Tokunaga et al. [28] of the University of Tsukuba reported a unique technique to remove infected pacemaker leads under median sternotomy. This technique might be useful for the patients with infected pacemaker leads, of which removal was a failure using the Excimer Laser Sheath Extraction System.

Contact sensitivity to components of devices after pacemaker implantation is a rare complication, but, once occurring, the treatment is difficult. The use of an expanded polytetrafluoroethylene (ePTFE) sheet wrapping is reported to be effective, but there are few published data on the long-term efficacy of this method. Yashiro et al. [29] of the Tokyo Women's Medical University retrospectively investigated the occurrence rate of allergies and other complications after this treatment.

Artificial valve

Suzuki et al. [30] reported the hemodynamic characteristics of expanded polytetrafluoroethylene (ePTFE) pulmonary valves with bulging sinuses quantitatively in a pediatric pulmonary mechanical circulatory system. Relationships between the leaflet movements and fluid characteristics were evaluated based on engineering analyses using echocardiography and a high-speed video camera. They revealed that the valve with bulging sinuses had the Reynolds number of 1667, and decreased the hydrodynamic energy loss and increased the systolic opening area.

Li et al. [31] studied the role of vortices in occurrence of cavitation associated with the closing motion of mechanical valves. They measured flow velocity distribution at valve closing to find that vortices themselves play a minor role in cavitation formation.

Hayashi of Niigata University reviewed the superiority of prosthetic heart valves including Starr–Edwards caged ball valves, Omniscience aortic tilting disc valves, and St. Jude Medical bileaflet valves, based on a single hospital experience of heart valve implantation from 1965 to 2009 in Niigata University Hospital. This review discusses the prominent antithrombogenicity of the Starr–Edwards model 1200 aortic prosthesis under selected conditions, the relatively rare thrombosed (despite its decreased opening angle) Omniscience aortic valve, the long-term outcomes of 10 as well as 30 years after St. Jude Medical valve replacement, and finally the latest results on the significance of patient–prosthesis mismatch in relation to myocardial hypertrophy [32].

Eguchi [33] commented on Hayashi's review. He showed the case with the long-term durability of classical caged ball valves (Starr–Edwards ball valve model 6120) implanted in May 1969 and removed at autopsy in June 2009 (40 years later). The patient, a 38-year-old woman who suffered from mitral stenosis and secondary tricuspid regurgitation, received successful mitral valve replacement and tricuspid valve repair, and did well for a long time without major complications, including cerebral thromboembolism. Macroscopic examination of the explanted ball valve showed multiple small spots of lipid infiltration on the surface of the brownish-yellowed silicone rubber ball of the explanted ball valve, with no cracks or distortion. The metallic cage was also free from structural deterioration.

Fukui et al. [34] of the Hyogo College of Medicine examined the outcomes in dialysis patients undergoing aortic valve replacement (AVR). In 38 consecutive dialysis patients who underwent AVR (mean age 69.1 ± 9.4 years; 23 bioprostheses and 15 mechanical valves), the operative mortality and the long-term survival were not different between the bioprosthesis and the mechanical valve group (13.0 vs. 13.3 %). The significant multivariate predictors for long-term survival were concomitant coronary artery bypass grafting (CABG) and prosthesis size. Valve types and age at operation did not affect long-term survival. Five-year survival of patients with small prosthetic valves and concomitant CABG was 0 %. They concluded that it may be appropriate to use a bioprosthesis in a dialysis patient with a small annulus and concomitant CABG even if the patient is young, when the patient's quality of life is taken into account.

Sugiki et al. [35] of Hokkaido University had reported the method to detect malfunctioning bileaflet valves (MBVs) with wavelet analysis system in bileaflet mechanical valve closing sound. They discussed the possibility of a new criteria for detecting MBVs, based on the scalographic properties of two spikes of bileaflet valve closing sound. Measuring both anterior spike area (Aa) and posterior spike area (Pa) for calculating the spike area ratio (Aa/Pa), they determined the cutoff value of Aa/Pa to be 1.4. They concluded the combination of a single spike on the scalogram and an Aa/Pa of >1.4 detected more MBVs than previously proposed criteria.

Li et al. [36] of Tamkang University studied the numerical comparison of the closing dynamics of a new trileaflet valve and the St. Jude Medical bileaflet valve. They focused on the closing velocity of the leaflets that is closely related to the cavitation. The closing velocity of the trileaflet valve was clearly slower than that of the St. Jude Medical bileaflet valve, and it would effectively reduce risk of damages to red blood cells and platelets.

Biomaterials

Recent advances in the fabrication technique of metallic materials have made possible commercialization of custom-made orthopedic implants. Okazaki et al. [37] reviewed the current concepts and trends of custom-made orthopedic implants, focusing on mechanical compatibility and biocompatibility of the osteosynthetic devices.

Sukmana [38] reviewed recent advances and future challenges in developing and using bioactive polymer scaffolds to promote tissue construct vascularization. In this review, various polymers such as synthetic polymers, collagen, alginate, hyaluronic acid and fibrin were introduced using 107 references.

Tissue engineering

Miyazawa et al. [39] reported and reviewed tissue engineering techniques to extrahepatic bile duct regeneration. They applied a bioabsorbable polymer tube as a bypass graft and autologous bone marrow cells were incorporated. They found neo-bile duct formation after 6 months implantation in pocine.

Yanagi et al. [40] reviewed regulatory frameworks for cell therapy products in Japan. Physicians may investigate new cell therapy products as a clinical research with the provisions of the Medical Practitioners Act. However, to obtain marketing approval, results of a clinical trial under Pharmaceuticals Affairs Act must be attached. They also outlined the review process of a new drug/device application for cell therapy products referring to the case of JACE®, the first approved commercial cell product in Japan.

Nakamura et al. [41] reported that low-molecular-weight heparin/protamine microparticles (LH/P MPs) are useful as biodegradable carriers for the controlled release of various growth factors contained in the frozen/thawed platelet-rich plasma (PRP). One day after induction of ischemia in adult BALB/c-nu/nu male mice, PRP/LH/P MPs solutions were administered into several sites of the ischemic hind limb intramuscularly. Seven days later, PRP/LH/P MPs-treatment led to the improved oxygen saturation. The limb survival rate at 1 year in the ischemia-induced mice injected with PRP/LH/P MPs was much higher than the control groups and reached approximately 25 %.

Dialysis

Jelicic et al. [42] reported the significant negative correlation between effluent IL-6 and daily diuresis and that the concentrations of effluent IL-6 were significantly higher in patients with RRF <2 ml/min compared with those with RRF ≥2 ml/min in patients treated with peritoneal dialysis. They concluded that local inflammation has an impact on the amount of diuresis in patients on CAPD.

Hirano et al. [43] reported the effect of fiber packing density on the dialysis fluid flow and blood flow, and on the dialysis performance of a hollow fiber dialyzer. They concluded that higher packing densities and lower housing diameters of the dialyzer resulted in higher dialysis performance because the dialysis fluid and blood entered smoothly and, hence, increased contact area between the dialysis fluid and the blood leading to better dialysis performance.

Tang et al. [44] of West China Hospital of Sichuan University reported the efficacy of the combined plasma exchange and continuous veno-venous hemofiltration therapy (CBPT) for treating acute fatty liver of pregnancy

(AFLP) complicated with acute kidney injury (AKI). The CBPT may contribute to an improvement in outcome for AFLP patients with AKI. They claimed that this technique should be used as soon as possible following the manifestation of oliguria, anuria, azotemia, hyperkalemia, and other life-threatening complications in AFLP patients.

Sakiyama et al. reported a positive relationship between the internal filtration rate (QIF) and the blood flow rate (QB) in a high flux dialyzer with a polysulfone membrane.

They also reported the dependence of the solute clearance on QB decrease with increasing molecular size of solute according to the decrease diffusivity through the membrane [45].

Sekiguchi et al. [46] studied the possible role of bone marrow derived cells in the repair of peritoneal fibrosis, resulting from long-term peritoneal dialysis. The GFP-transgenic mouse bone marrow (BM) cells in several lineages were isolated and injected into the peritoneal cavity of C57Bl/6 mice after repeated chlorhexidine gluconate (CG) stimulation. Not only infiltrating peripheral BM cells, but also the administered BM cells seems to be differentiated into mesothelial cells in the peritoneal repair. The intraperitoneal administration of the immature BM-derived cells may be a possible strategy for interruption of the vicious cycle in the damaged peritoneum after discontinuation of PD.

Artificial liver, pancreas

Mibu et al. [47] of the Kochi Medical School Hospital reported the efficacy and safety of the artificial pancreas through the workload of ICU nurses. The artificial pancreas could continuously monitor the blood glucose levels and maintain them at appropriate levels without hypoglycemia. The management of blood glucose with an artificial pancreas in the ICU reduced the workload of ICU nurses compared to the conventional sliding-scale method. Therefore, they claimed that the artificial pancreas can be a useful device for the management of blood glucose in the ICU.

Sasamoto et al. [48] reported the effects of EDT324 solution on the vitrification of isolated rat islets of Langerhans. The EDT324 solution was consisted of ethylene glycol, DMSO, trehalose and RPMI. They concluded that cryopreservation using EDT324 solution is an alternative to commonly used vitrification solutions, such as DMSO.

Artificial skin, muscle, bone, neuron

Taniguchi et al. [49] reported successful clinical results of allogenic cultured dermal substitutes for the treatment of eight patients with intractable skin ulcers who had various underlying diseases, including diabetes mellitus, systemic lupus erythematosus, antiphospholipid syndrome, necrobiosis lipoidica, stasis dermatitis, livedo vasculopathy, and rheumatoid arthritis.

Sakaguchi et al. [50] investigated the surgical procedures involved in the implantation of a newly developed direct optic nerve electrode device for inducing artificial vision in rabbits. The electrode device comprised seven wire stimulation electrodes and a return electrode, which were inserted into the vitreous cavity using a trocar through a scleral incision, and were set into the optic disc with no damage in one step within 10 min. They confirmed that their surgical procedures were useful for the artificial vision system because electrically evoked potentials were recorded at the visual cortex when the electrodes were stimulated.

Others

Transcatheter closure of atrial septum defect (ASD) with a closure device is increasing, but the long-term safety of this device remains unproved. Tomizawa of the Tokyo Women's Medical University reviewed the complexity of this device and proposed the need for a world-wide registry system of this procedure [51].

Aodai et al. [52] proposed a new method of adhesion using the integrated low-level energy sources of heat, vibration, and pressure. This adhesion method can be used to attach biological tissue to a metal object. Effects of surface roughness and energy of the metal subject on adhesion performance were studied in this paper. A porcine aorta was adhered to sandblast-treated stainless steel by use of an adhesion temperature of 80 °C, a vibration amplitude of 15 μm, a pressure of 2.5 MPa, an adhesion time of 120 s, and a surface roughness of an Ra 0.25 μm. The adhesion performance was improved by roughening the surface of the metal specimen. Surface energy has an insignificant effect on adhesive strength. The adhesion performance varied depending on metal material for the same surface roughness, Ra, and energy.

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ORIGINAL ARTICLE

Change in myocardial oxygen consumption employing continuous-flow LVAD with cardiac beat synchronizing system, in acute ischemic heart failure models

Akihide Umeki · Takashi Nishimura · Yoshiaki Takewa · Masahiko Ando · Mamoru Arakawa · Yuichiro Kishimoto · Tomonori Tsukiya · Toshihide Mizuno · Shunei Kyo · Minoru Ono · Yoshiyuki Taenaka · Eisuke Tatsumi

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Abstract Aiming the 'Bridge to Recovery' course, we have developed a novel left ventricular assist device (LVAD) controlling system. It can change the rotational speed of the continuous flow LVAD, EVAHEART, synchronized with the cardiac beat. Employing this system, we have already demonstrated that myocardial oxygen consumption (MVO2), which is considered to be equivalent to native heart load, changes in the hearts of normal goats. Herein, we examined changes in goats with acute ischemic heart failure. We studied 14 goats (56.1 ± 6.9 kg) with acute ischemic heart failure due to coronary microsphere embolization. We installed the EVAHEART and drive in four modes: "circuit-clamp", "continuous support", "counter-pulse", and "co-pulse", with 50 and 100 % bypass. In comparison to the circuit-clamp mode, MVO2 was reduced to 70.4 ± 17.9 % in the counter-pulse mode and increased to 90.3 ± 14.5 % in the co-pulse mode, whereas it was 80.0 ± 14.5 % in the continuous mode, with 100 % bypass ($p < 0.05$). The same difference was confirmed with 50 % bypass. This means that we may have a chance to change the native heart load by controlling the LVAD rotation in synchrony with the cardiac rhythm, so we named our controller as the Native Heart Load Control System (NHLCS). Employing changeable MVO2 with NHLCS according to the patient's condition may provide more opportunity for native heart recovery with LVAD, especially for patients with ischemic heart diseases.

Keywords Continuous-flow LVAD · NHLCS · Myocardial oxygen consumption · Synchronized with cardiac beat

A. Umeki · T. Nishimura · M. Ando · S. Kyo · M. Ono
Department of Cardiothoracic Surgery, The University of Tokyo, Tokyo, Japan

A. Umeki · Y. Takewa · M. Arakawa · Y. Kishimoto · T. Tsukiya · T. Mizuno · Y. Taenaka · E. Tatsumi
Department of Artificial Organ, National Cerebral and Cardiovascular Center, Suita, Japan

A. Umeki (✉)
5-8-7-104 Honkomagome, Bunkyou-ku, Tokyo, Japan
e-mail: phoenix@kkf.biglobe.ne.jp; louvre1974@yahoo.co.jp

T. Nishimura (✉) · S. Kyo
Department of Therapeutic Strategy for Heart Failure, The University of Tokyo, 7-3-1 Hongo, Bunkyou-ku, Tokyo, Japan
e-mail: takashin-tky@umin.ac.jp

T. Nishimura · S. Kyo
Department of Cardiothoracic Surgery, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan

Introduction

Patients with severe heart failure are treated with a multidisciplinary approach involving conservative medical management, and prognoses have improved remarkably in recent years. And some patients who are resistant to current medical treatments are considered to have indications for left ventricular assist device (LVAD) implantation or heart transplantation. But, given the scarcity of donor hearts available in Japan, the number of patients with LVAD for severe chronic heart failure is rapidly increasing. Thus, there is an urgent need to establish methods which can improve the courses of patients with LVAD, especially aiming for the 'Bridge to Recovery' course (BTR) with the recovery of the native heart function [1–5].

Obviously, now is the time for continuous-flow LVAD. Due to its small size, this LVAD can be installed inside the body. Patients can be discharged from the hospital, and the

risk of infection would thus presumably be reduced. The favorable clinical outcomes add impetus to this trend [6]. On the other hand, many reports comparing the systemic effects of pulsatile and continuous-flow LVAD have not described favorable results [6–27]. We consider the merit of our novel system to be its potential ability to provide physiological circulation.

Given this situation, we developed and introduced a power-control unit for centrifugal LVAD, the EVAHEART (Sun Medical, Nagano, Tokyo, Japan) [28, 29]. With this unit, we drive the EVAHEART in synchrony with the native rhythm of the heart, by adjusting the time span and the rotational speed (RS) in the systolic and diastolic phases [30–36]. Ours is the first trial to evaluate continuous-flow LVAD with the pulsatile driving technique. Apparently, the LVAD can decrease the native heart load by aiding native heart function, and decreasing left ventricular end-diastolic pressure and volume. The most suitable parameter for evaluating the native heart load is myocardial oxygen consumption (MVO2), because it reflects precisely the left ventricular pressure volume area (PVA), which is considered to be energetically equivalent to the sum of external energy and potential energy [37–41]. There are many reports showing the effect of reducing the native heart load employing LVAD [42–46]. In these reports, MVO2 was reduced by LVAD, regardless of whether it was continuous [42–44] or pulsatile [45, 46]. In addition, this trend does not depend on the condition of the native heart. This effect has been confirmed in both normal [42, 44, 46] and failing [43, 45] hearts.

Thus, we have recently focused on MVO2 in order to evaluate our novel system, and found that MVO2 can be altered according to the control mode in goats with normal hearts [31]. If we can achieve an appropriate amount of MVO2 by controlling the rotation of continuous-flow LVAD, in synchrony with the cardiac beat, we may have the opportunity to enhance the function of the native heart supported by LVAD. However, before application in a clinical situation, it is necessary to test this design in models of heart failure, which might be completely different from normal heart models. Therefore, in the present study, we examined changes in MVO2 in goats with acute ischemic heart failure. Herein, our aim is to show that MVO2 can be changed employing our novel control method in an acute ischemic heart failure model.

Materials and methods

Animals

We studied 14 goats with acute ischemic heart failure (56.1 ± 6.9 kg) due to coronary microsphere embolization. The animals used in this study were maintained in accordance with the guidelines of the Committee on Animal Studies at the National Cerebral and Cardiovascular Center. This study was approved by the National Cerebral and Cardiovascular Center Animal Investigation Committee. Institutional guidelines for the care and use of laboratory animals have been observed.

Surgical procedures, implanted devices

The animals were tranquilized with ketamine hydrochloride (8–10 mg/kg intramuscularly) and then intubated and mechanically ventilated. The goats were anesthetized with isoflurane (1–3 vol/100 ml in oxygen), and then draped and prepped in the right lateral recumbent position. A left thoracotomy was performed and the fifth costal bone was resected. We retained the left intra-thoracic artery and vein to measure the aortic pressure (AoP) and the central vein pressure (CVP), and also to collect data for blood gas analysis. The blood flows in the ascending aorta, LVAD, and coronary artery (left main trunk, LMT) were measured using a flow meter. We used an electromagnetic flow meter (16–22 mm in diameter, EMF-1000, Nihon Kohden, Tokyo, Japan) for the aorta, an ultrasonic flow meter (3–4 mm, HQD3FSB, Transonic Systems, Ithaca, NY, USA) for the LMT, and another ultrasonic flow meter (16 mm, TS420, Transonic Systems) for the LVAD. After heparinization (200 U/kg), centrifugal LVAD, EVAHEART was installed. Inflow cannula was inserted from the left ventricular apex and the outflow conduit was to the descending aorta. A 6Fr conductance catheter (2S-RH-6DA-116, Taisho Biomed Instrument, Osaka, Japan) and a 4Fr micro-tip catheter pressure transducer (Millar Instruments, Houston, TX, USA) were inserted into the left ventricle from the anterior wall to collect data for the pressure volume curve of the left ventricle. Because the coronary sinus is connected to the accessory hemiazygos vein in goats, we inserted a Sarns retrograde cannula (10Fr, Terumo corp., Tokyo, Japan) into the coronary sinus from the accessory hemiazygos vein and thereby sampled coronary sinus vein blood. We calculated the MVO2 by multiplying the difference in oxygen saturation between the artery (ScaO2) and coronary sinus blood (ScvO2), the hemoglobin concentration of arterial blood (aHb), and the amount of coronary flow (CoF) ($MVO2 = (ScaO2 - ScvO2) \times 1.34 \times aHb \times CoF$). The aforementioned vital data were recorded in Labchart5 (ADInstruments, Bella Vista NSW, Australia).

Making left ventricular dysfunction models

To create the acute ischemic heart failure model, we microembolized the left anterior descending coronary artery

(LAD), as described in earlier reports [47–50]. A multipurpose Judkins catheter (4Fr, Create Medic Co., LTD, Japan) was introduced through a long sheath (4Fr × 17 cm) into the left carotid artery toward the LAD under fluoroscopic guidance. We then injected approximately 0.3 million (0.005 million/kg) microspheres (50 μm in diameter) into the LAD. Ten minutes after this injection, we observed the animal's general condition, including aortic flow. If aortic flow exceeded 60 % of the baseline value, we arbitrarily added half the amount of microspheres (0.0025 million/kg), to achieve a total amount of 0.30 ± 0.14 million. After 30 min of further observation, we collected data to assure stable optimal cardiac function. We planned to reduce and then maintain cardiac output at approximately 60 % of the native heart function documented prior to creation of the acute ischemic heart failure model.

Study protocol, LVAD control method

We controlled the AoP and CVP to ensure stable conditions during the examination. This assured that there were no changes in the afterload or the preload of the heart. Heart rate was also controlled. We controlled these values by adjusting the volume of infusion and changing the depth of anesthesia, not by using either vasodilators or catecholamines. We used 2 % lidocaine (1 mg/kg/h) and Nifekalant hydrochloride (0.4 mg/kg/h) during the experiment to prevent ventricular arrhythmias.

We previously reported the details of our novel pump controller, which can change the RS of the EVAHEART in synchrony with the cardiac cycle [30–36]. We defined the systolic phase as 35 % of the RR interval and the diastolic phase as 65 % of the RR interval, and we input the duration of each phase according to the heart rate. Our controller can change the RS of each phase, detecting the R wave from an electrocardiogram (ECG). The bypass rate (BR) was calculated by dividing the pump flow rate (PF) by the sum of the PF and aortic flow (AoF) rates.

Using this controller, we compared four driving modes in this study. The first was the "circuit-clamp" (pump-off) mode, clamping the LVAD circuit so as to evaluate the conditions of the native heart. The next was the "continuous support" mode, driving the LVAD continuously at a stable RS. This is the mode we usually apply in clinical situations. The third was the "counter-pulse" mode, in which we set the RS of the systolic phase to approximately 700 rpm, the minimum speed of the LVAD system, and adjusted the RS of the diastolic phase to achieve the most appropriate BR, as needed. In this study, the BRs were set at 50 and 100 %. The latter was the "co-pulse" mode. This mode was defined in an opposite manner; we set the RS of the diastolic phase to approximately 1,000 rpm so as to avoid inducing a reverse flow inside the LVAD circuit, and adjusted the RS of the systolic phase to achieve BRs of 50 and 100 % (Fig. 1). We obtained the various data at 5 min after setting each mode. This was considered to be a sufficient period for the animal's condition to stabilize. In this study, we mainly evaluated the MVO2. The comparison was performed by repeated analysis of variance followed by Tukey's multiple comparison test, and *a p* value less than 0.05 was considered as statistically significant.

Results

Sample waveforms of the ECG, AoP, CVP, left ventricular pressure (LVP), PF, AoF, CoF, RS, and the BR are shown in Fig. 2. In the continuous mode, the output of the native heart (AoF) was decreased by removing blood with the LVAD. The pulse pressure was also reduced as compared to that of the circuit-clamp mode. In the counter-pulse mode, increased RS in the diastolic phase produced much gentler AoP waveforms than those obtained with the continuous or the circuit-clamp mode. The gentle waveform resulted from a counter-pulse effect, much like that seen with intra-aortic balloon pumping, as we expected.

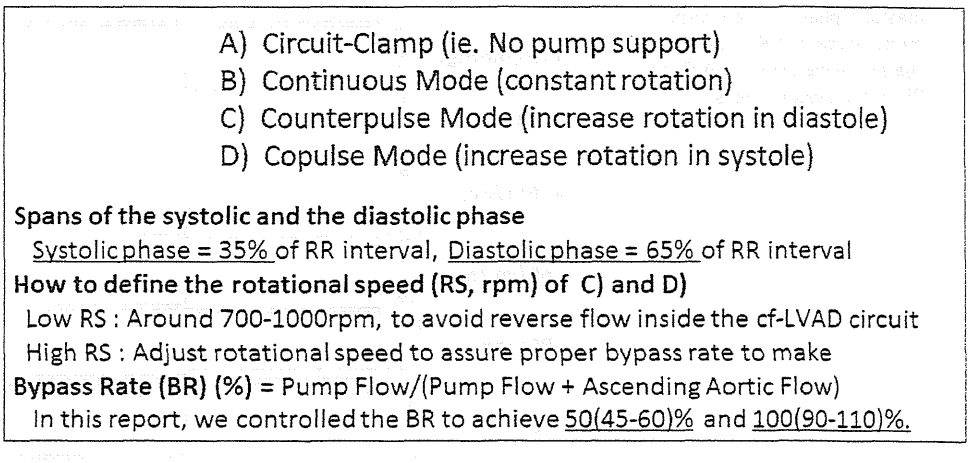


Fig. 1 Driving modes of NHLCS. We compared MVO2 in 4 modes: "circuit-clamp", "continuous support", "counter-pulse" (to raise RS in diastole), and "co-pulse" (to raise RS in systole), with 50 and 100 % bypass. We defined the systolic phase as 35 % of the RR interval and the diastolic phase as 65 % of the RR interval, and set the upper rotational speed so as to achieve an appropriate bypass rate, as needed

Although the PF waveform became almost flat, there was no change in the total amount of PF among the three driving modes (except the circuit-clamp mode). The amount of CoF in the diastolic phase was higher than with the other modes due to the counter-pulse effect. By contrast, in the co-pulse mode, the waveforms of AoP and PF were more precipitous than with the other mode, due to the higher RS in the systolic phase. The amount of CoF in the diastolic phase was lower than with the other three modes.

Hemodynamic parameters are presented in Table 1. Heart rate (HR), CVP, AoP, LVP, total flow (the sum of AoF and PF), and the BR are shown. The baseline data (before heart failure) are on the left, and those of acute ischemic heart failure models with each of the driving modes and BRs are on the right. In the right table, the total flow amount in the circuit-clamp mode is equivalent to native heart output with acute heart failure. The parameters shown are essentially 60 % of the baseline data. This means the amount of native heart output was reduced to approximately 60 %, as we expected. Considering the differences among driving modes with LVAD (other than the circuit-clamp mode), there were no significant differences in these hemodynamic parameters.

Figure 3 shows the MVO2 in each mode as a percentage of that in the circuit-clamp mode (=100 %). The MVO2 was decreased in continuous mode as compared to the circuit-clamp mode, regardless of the BR. This means that the LVAD would reduce the load on the native heart in the setting of acute heart failure. Comparing the MVO2 among each of the driving modes, it was lower in the counter-pulse mode and higher in the co-pulse mode than in the continuous mode ($p < 0.05$) at both the 50 and the 100 % BR. With the 50 % BR, the MVO2 was 83.9 ± 14.8 % in the counter-pulse mode and 100.8 ± 9.0 % in the co-pulse mode, whereas it was 92.2 ± 9.0 % in the continuous support mode (Fig. 3a). The same trend was detected with the 100 % BR, where the MVO2 was 70.4 ± 17.9 % in the counter-pulse mode and 90.3 ± 14.5 % in the co-pulse mode, whereas it was 80.0 ± 14.5 % in the continuous support mode (Fig. 3b).

Figure 4 shows the end-diastolic volume of the left ventricle (EDV) in each mode as a percentage of that in the circuit-clamp mode (=100 %). The EDV was lower in the counter-pulse mode and higher in the co-pulse mode than in the continuous mode ($p < 0.05$) for both the 50 and the 100 % BR. With the 50 % BR, the EDV was 94.8 ± 3.5 % in the counter-pulse mode and 100.3 ± 3.3 % in the co-pulse mode, whereas it was 97.3 ± 3.1 % in the continuous support mode. The same trend was detected with the 100 % BR, where the EDV was 83.2 ± 8.2 % in the counter-pulse mode and 93.4 ± 8.0 % in the co-pulse mode, whereas it was 88.3 ± 8.6 % in the continuous support mode.

Figure 5 shows the echocardiographic images of the left ventricle in the end-diastolic phase. The upper chamber was the left ventricle, and the inflow cannula was inserted from the apex. The size of the left ventricle was significantly decreased in the counter-pulse mode (Fig. 5b) and increased in the co-pulse mode (Fig. 5c) as compared with that in the continuous mode (Fig. 5a).

Pressure volume curves for the left ventricle in the each of the modes with acute heart failure are shown in Fig. 6.

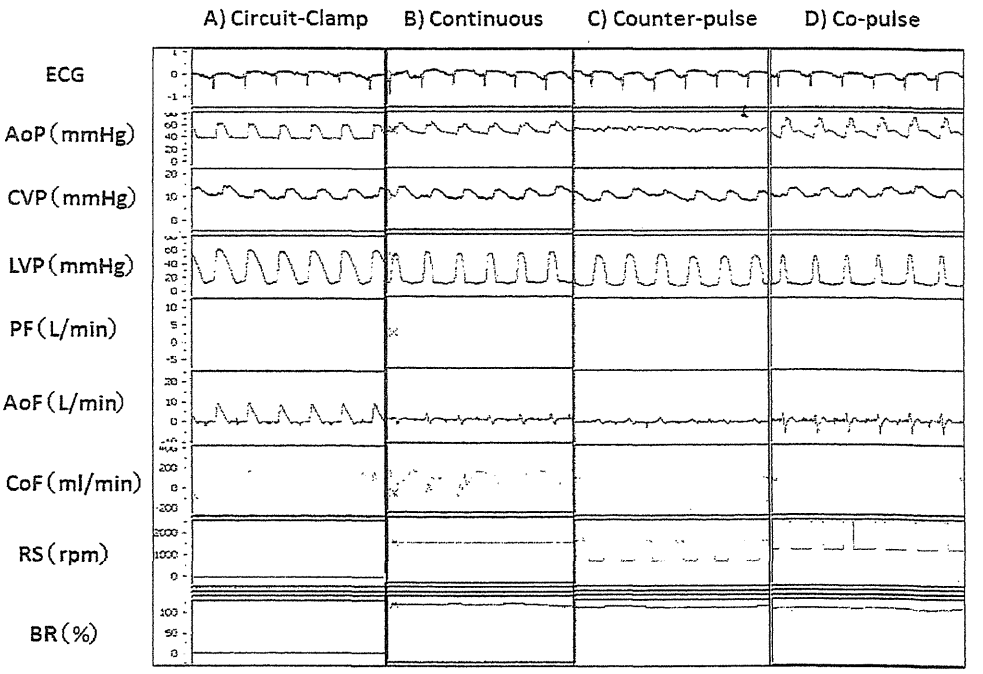


Fig. 2 Waveforms of pressure and flow. *PF* pump flow, *AoF* ascending aortic flow, *CoF* coronary flow, *RS* rotational speed, *BR* bypass rate. In the counter-pulse mode, increased RS resulted in gentler waveforms of AoP and PF in the diastolic phase. In the co-pulse mode, increased RS resulted in sharper waveforms of AoP and PF in the systolic phase

Table 1 Vital data at baseline and after embolization in each mode

Baseline Data	
HR	76.3 ± 11.7
Mean CVP (mmHg)	11.2± 5.6
Mean AoP	74.6 ± 14.7
Mean LVP	54.1± 14.9
Pump Flow(L/min)	0.0 ± 0.0
Total Flow (L/min)	4.8 ± 1.2
Bypass Rate (%)	0.0 ± 0.0

50% Bypass	Circuit-Clamp	Continuous	Counter-pulse	Co-pulse
HR	80.6 ± 14.6	81.9 ± 15.6	79.2 ± 12.9	81.9 ± 12.4
Mean CVP(mmHg)	14.6± 4.4	12.3 ± 4.0	13.2 ± 4.8	14.3 ± 3.7
Mean AoP(mmHg)	66.7 ± 16.8	61.5 ± 10.3	62.3 ± 11.6	60.8 ± 10.9
Mean LVP(mmHg)	46.3± 13.0	41.4 ± 8.8	40.8 ± 12.9	39.9 ± 12.4
Pump Flow(L/min)	0.0 ± 0.0	1.6 ± 0.8	1.7 ± 0.7	1.6 ± 0.9
Total Flow (L/min)	3.0 ± 1.1	3.4 ± 1.0	3.5 ± .0.9	3.4 ± 1.2
Bypass Rate (%)	0.0 ± 0.0	53.4± 8.4	52.6 ± 9..3	53.1 ± 8.6

100% Bypass	Circuit-Clamp	Continuous	Counter-pulse	Co-pulse
HR	83.4± 14.0	83.0 ± 13.1	80.9 ± 12.6	82.6 ± 10.7
Mean CVP (mmHg)	11.4 ± 6.4	9.8 ± 4.9	10.6 ± 5.7	10.4 ± 6.0
Mean AoP (mmHg)	61.4 ± 12.3	58.4 ± 8.4	59.2 ±9.6	60.5 ± 10.0
Mean LVP (mmHg)	45.4 ± 13.2	40.1 ± 10.3	39.6. ± 11.2	40.6 ± 10.5
Pump Flow(L/min)	0.0 ± 0.0	4.0 ± 1.2	4.1 ± 1.4	3.8 ± 1.0
Total Flow (L/min)	2.8 ± 1.3	3.8± 1.4	4.0 ± 1.3	3.7± 1.2
Bypass Rate (%)	0.0 ± 0.0	108.2 ± 10.1	106.4± 9.8	105.3 ±8.8

Bypass rates were adjusted to 50 or 100 % for each mode. Aortic flow in the circuit-clamp mode was decreased to approximately 60 % of the baseline value. There were no significant differences from the data obtained with LVAD

Inferior vena cava occlusion was performed to make the loop. The vertical axis is the left ventricular pressure, and the horizontal axis is the left ventricular volume. The left ventricular EDV was increased in the co-pulse mode (rightward shift), and was decreased in the counter-pulse mode (leftward shift). External work is equivalent to the area enclosed by the pressure volume curve. This is also decreased in the counter-pulse mode, and increased in the co-pulse mode as compared to the continuous mode.

Discussion

With the goal of improving the function of the native heart employing LVAD, and allowing patients a BTR course, we developed a novel driving system, the Native Heart Load Control System (NHLCS), for continuous-flow LVAD. The first concern at the development was the effect of LVAD pulsatility. Many reports have compared clinical outcomes or effects on circulatory dynamics between pulsatile and continuous-flow LVAD [6–27]. The norepinephrine level, which is higher in the non-pulsatile than in the pulsatile LVAD, may affect oxygen metabolic conditions and worsen systemic oxygen uptake in the acute phase [10–13]. The systemic vascular resistance response to norepinephrine decreased markedly with non-pulsatile flow. From the viewpoint of hemodynamic change, pulsatile flow generates more energy, which may be beneficial for vital organ perfusion [14], with the amount depending on the timing of mechanical cardiac beating [15, 16]. Pulsatile flow may be beneficial for the end-organ micro-circulation [17] and for coronary flow [18], but the effect on brain metabolism remains a source of controversy [20–22]. The vascular system is also affected by pulsatility [23]. Structural change in the aortic wall, caused by atrophy of aortic smooth muscle cells, occurs with non-pulsatile flow [24–27]. In summary, the overall systemic effects of long-term support with continuous LVAD have yet to be determined. We simply do not know which effects, if any, are beneficial or harmful. However, as to clinical outcomes, unfavorable results with pulsatile LVAD have been reported [6]. These may, however, arise from the higher risks of complications with pulsatile LVAD. In our view, the ability of pulsatile LVAD to provide physiological circulation is a benefit that cannot be denied.

Thus, we developed the NHLCS, with which we can drive the continuous-flow LVAD synchronized with the actual cardiac rhythm. Our recent report was the first description of such a pulsatile driving technique [30–36]. Herein, we aimed to confirm the effect of this system on the native heart load from the aspect of MVO2, which we consider to be the most important factor in evaluating native heart load changes. The pressure–volume area (PVA) is defined as the area framed by the lines of the end-diastolic and systolic pressure volume relationship and the pressure–volume curve of the systolic phase. The rectangular area within the pressure volume loop represents the external work performed, and the triangular area under the Emax line (end-systolic slope of the pressure volume relationship as maximum elastance) represents the elastic potential energy stored in the left ventricle. Therefore, PVA is considered to be equivalent to the sum of external work and potential energy. Furthermore, PVA is known to show a strong positive correlation with MVO2. [37–41] Thus, the MVO2, the amount of oxygen used by the left ventricle, is closely related to cardiac energy dynamics, and is the most useful factor for evaluating the native heart load. The MVO2 is the optimal parameter to represent

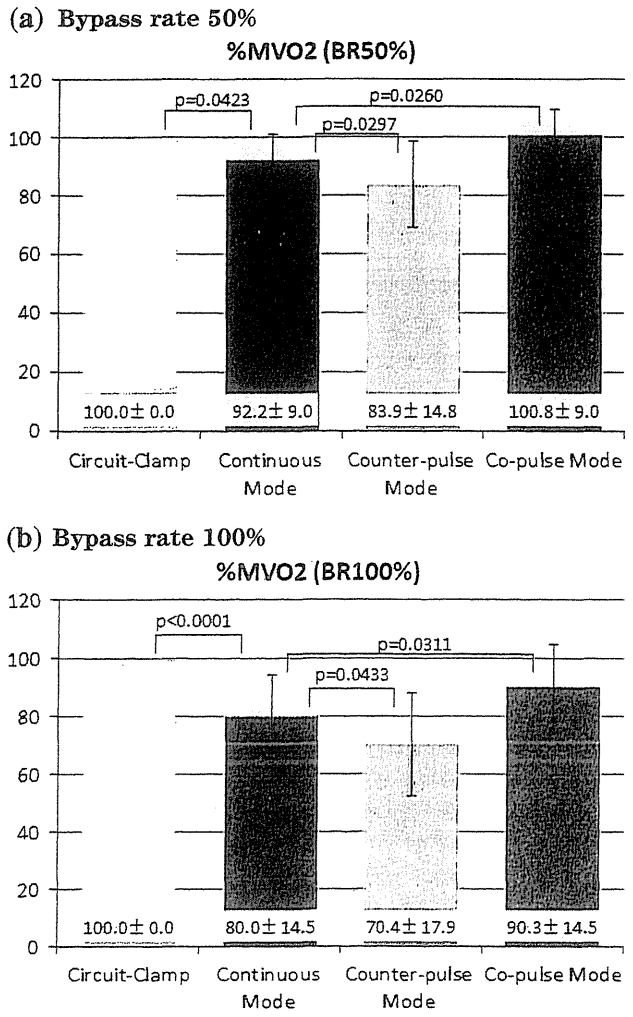


Fig. 3 Amount of myocardial oxygen consumption (circuit-clamp = 100). The amount of MVO2 was decreased by LVAD in acute ischemic heart failure models. MVO2 decreased in the counter-pulse mode and increased in the co-pulse mode relative to the continuous mode ($p < 0.05$) for both the 50 % (Fig. 3a) and the 100 % (Fig. 3b) bypass rates

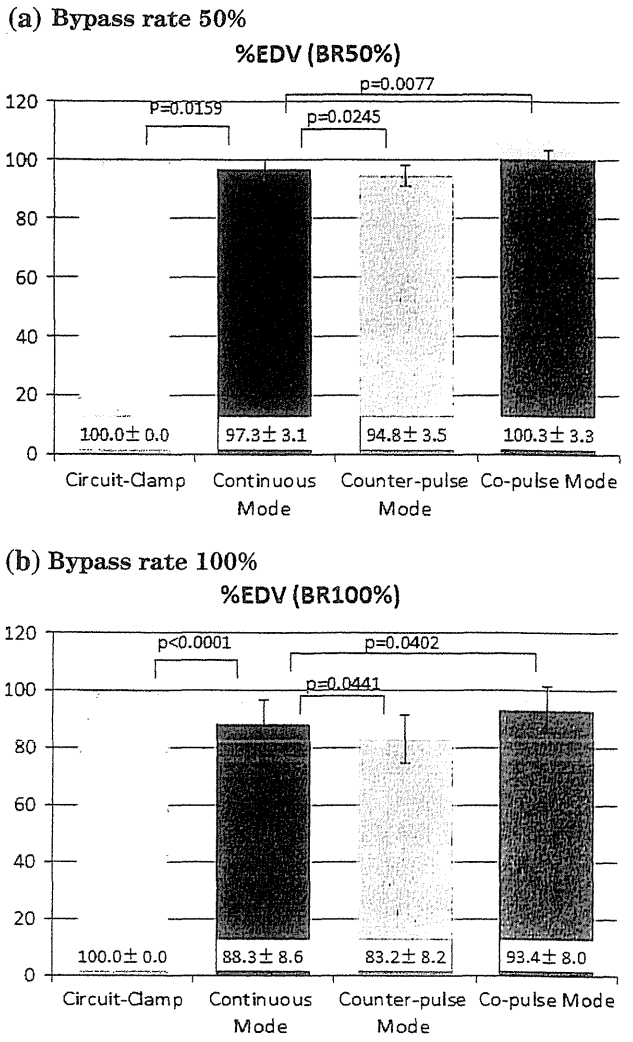
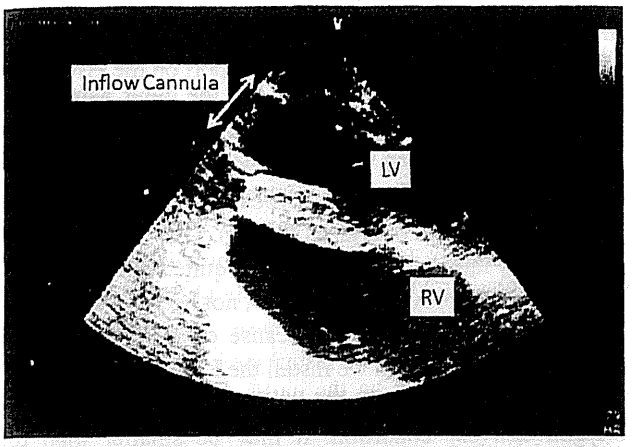


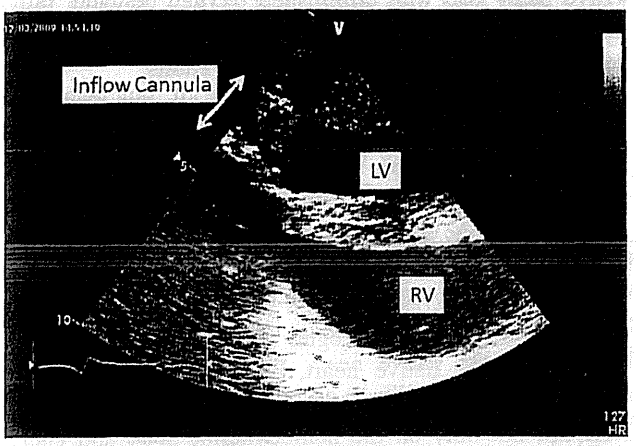
Fig. 4 Left ventricular end-diastolic volume in various modes (circuit-clamp = 100). EDV was decreased by LVAD. EDV decreased in the counter-pulse mode and increased in the co-pulse mode relative to the continuous mode ($p < 0.05$) for both the 50 % (Fig. 4a) and the 100 % (Fig. 4b) BR

oxygen utilization and energy use by the myocardium under ischemic conditions. This is why we chose MVO2 as the parameter for assessing the NHLCS effect on the native heart load. In addition, in this study, we aimed to evaluate the effect of NHLCS on acute heart failure models. In these models, the myocardial oxygen demand is inevitably higher than in normal heart models, due to the suppression of myocardial perfusion. High end-diastolic pressure and sympathetic hyperactivity with high catecholamine concentrations may greatly exacerbate these demands. However, in response to the increased oxygen requirements, low oxygen delivery may occur due to insufficient myocardial perfusion, caused by stenosis of the coronary artery itself, high intra-myocardial pressure, low blood pressure and so on. It is quite interesting to evaluate changes in the myocardial oxygen dynamic state with NHLCS under ischemic conditions.

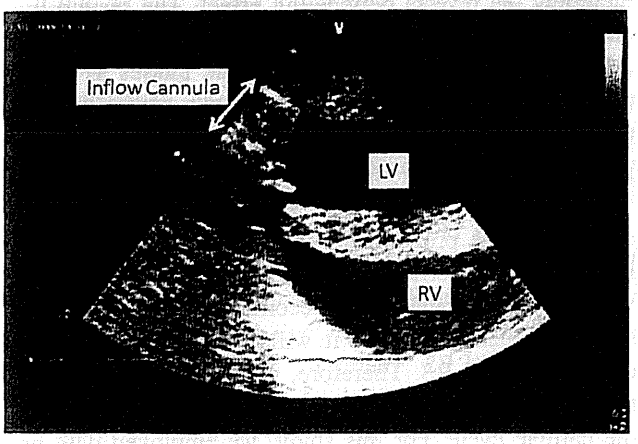
In such a situation, we have demonstrated the possibility of changing the MVO2 intentionally with our NHLCS. First, when comparing the circuit-clamp and continuous modes, MVO2 was decreased with LVAD whether the myocardium was ischemic or not. This result is consistent with the outcomes of other reports [42–46]. Simply put, this observation means that the native heart load is reduced with LVAD because it carries part of the burden on the native heart (external workload). This may partially be explained by the decrease in EDV with LVAD [41]. According to the Frank-Starling law of the heart, the external work applied against afterload relies upon the EDV. This means that cardiac energy metabolism is greatly



(a) Continuous mode

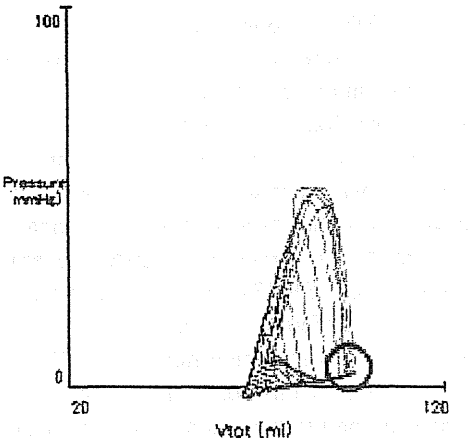


(b) Counter-pulse mode

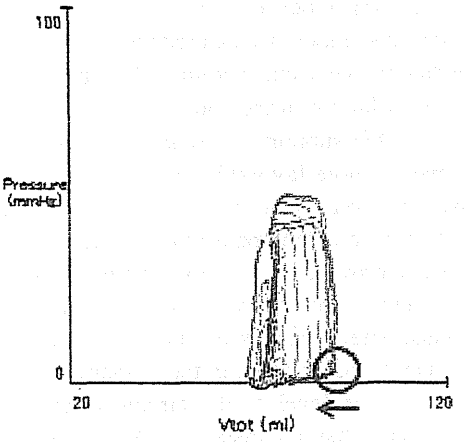


(c) Co-pulse mode

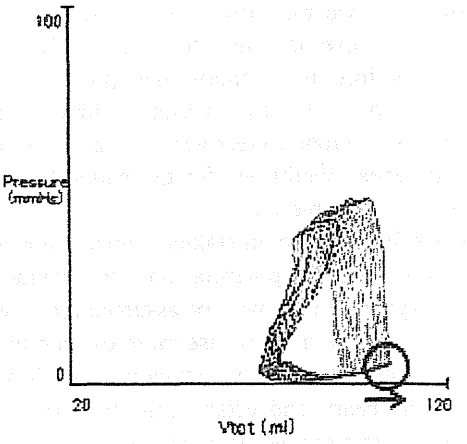
Fig. 5 Echocardiography of the end-diastolic phase (**a** continuous mode, **b** counter-pulse mode, **c** co-pulse mode). The size of the left ventricle was significantly decreased in the counter-pulse mode (**b**) and increased in the co-pulse mode (**c**), as compared with that in the continuous mode (**a**)



(a) Continuous mode



(b) Counter-pulse mode



(c) Co-pulse mode

Fig. 6 Samples of pressure volume loops in the continuous mode (**a**), counter-pulse mode (**b**) and co-pulse mode (**c**). The left ventricular end-diastolic volume (EDV) was increased in the co-pulse mode (*rightward shift*), and was decreased in the counter-pulse mode (*leftward shift*)

influenced by EDV. Theoretically, it is easy to understand that LVAD can decrease the native heart load and MVO2 via its volume unloading effect.

Changing our frame of reference to the difference in MVO2 between the two experimental driving modes, the MVO2 amount was decreased with the counter-pulse mode and increased with the co-pulse mode, as compared with the continuous mode. This trend was apparent regardless of the cardiac state or the BR [31], and the same trend was recognized for the difference in EDV [36]. The EDV was confirmed to be one of the determinants of MVO2, based on our present results. Considering the equivalence between MVO2 and the native heart load, the significance of this result is that we may have a chance to produce a desirable load suiting the condition of the native heart by choosing our novel driving mode of continuous-flow LVAD. With the counter-pulse mode, we can reduce the native heart load by unloading the ventricular volume for patients with acute ischemic heart failure in the counter-pulse mode. However, when full LVAD support is needed for a severely failing heart, it may be more favorable to choose the counter-pulse mode with its heart load reduction effect. Furthermore, raising RS in the diastolic phase may induce left ventricular unloading and provide an AoP boost-up effect, which would especially benefit patients with ischemia via its so-called counter-pulse effect mimicking that of intra-aortic balloon pumping. On the other hand, in the co-pulse mode, the load is increased to the level of the circuit-clamp mode, even though the heart has an installed LVAD. We can create more strain on the native heart by loading it with excess volume when we want to train the native heart, or to assess the possibility of weaning from the LVAD in the recovery stage. The strain level is almost the same as if the LVAD is detached. Therefore, if we choose the appropriate mode of NHLCS according to the various clinical situations encountered on the road to recovery, we may have a chance to create the ideal conditions for the native heart by providing the most suitable load.

These results may be mistakenly understood to mean that the LVAD has the potential only to provide a small amount of oxygen. It may well be assumed that it would be natural for the native heart to use more oxygen than in the condition without LVAD, after attaching the LVAD to the acute ischemic heart, and establishing the system to provide more CoF and oxygen to myocardium. However, this would simply be due to the decrease in myocardial oxygen demand, secondary to the reduced native heart load and the sufficient CoF. Especially with the counter-pulse mode, the oxygen demand may be decreased with the EDV and native heart load reductions. However, conversely, with the co-pulse mode, the demand may be increased.

Goldstein implicated various indices of energy metabolism, external work, PVA, the tension-time index, the integral of systolic force, and intra-cardiac pressure, as major determinants of MVO2, in a report on the effects of a low BR driving the LVAD [43]. On the other hand, there were no correlations between MVO2 and parameters associated with the oxygen delivery potential (AoP in diastole, the amount of CoF, and myocardial oxygen delivery [CoF × O2 content of arterial blood]). They also noted that the severely failing myocardium was quite sensitive to even the slight relief provided by LVAD, not because the oxygen supply was augmented, but because oxygen requirements were diminished. When we install the LVAD in an ischemic heart, MVO2 depends on the native heart load, not on the oxygen delivery condition. It may be smaller than that without LVAD, because of the substantial reduction in the native heart load with diminished oxygen demand, rather than because of an insufficient oxygen supply. These results are in good agreement with our observations.

This study has limitations. First of all, our results are based on an acute ischemic heart failure model, such that it is unclear whether the same results would apply to the chronically failing heart in clinical situations. However, the change in MVO2 depends on the ventricular hemodynamic state (EDV, etc.), as detailed above. Therefore, we believe the same trend would be seen in the chronically failing heart. We have already begun to evaluate the effects of NHLCS on the native heart, by creating chronic heart failure models. We aim to ascertain the chronic effects of NHLCS, not only on the hemodynamic state and energy metabolism, but also on tissues and genetic expressions including the reverse remodeling effect. The second limitation involves the mechanical factor. Herein, we defined the spans of the systolic and diastolic phases as 35 and 65 % of the RR interval based on our experience with goats. However, there may well be marked alterations in these parameters among individuals or according to the state of the native heart. In addition, the timing of synchronization is problematic, because the continuous-flow LVAD is characterized by the RS changing gradually, i.e., within minutes rather than seconds. If we incorporate a signal to change the RS, it will still take some time to obtain the ideal RS. Therefore, we must confirm whether the timings of the maximum or minimum RS are attuned to the cardiac cycle. For this study, we employed data with which the LVAD rotation was in synchrony with the heartbeat, in terms of span and timing. We are now endeavoring to adjust the system for NHLCS, which has the capacity to change the span and timing of synchronization according to the native heartbeat. The third limitation may be the site of the outflow graft. Usually, we place the outflow graft of the LVAD at the ascending aorta. In this study, however, we placed it in the descending aorta, because of the shortness of the ascending aorta in goats. These animals have a bovine carotid artery which diverges

from the ascending aorta near the base of the heart. Furthermore, all of the carotid and subclavian arteries bifurcate from this bovine artery. We will need to examine outflow grafts placed at the ascending aorta in the future. Although these differences may have impacted the cardiac after-load, many reports suggest equivalence between these outflow graft sites [51, 52].

Herein, we demonstrated the possibility of changing the native heart load employing NHLCS, based on changes in MVO2. This means that a desirable native heart load can be produced by choosing our novel driving mode of continuous-flow LVAD. We may thus be able to create the appropriate conditions for BTR. We can reduce the native heart load for patients with severe heart failure in the counter-pulse mode. On the other hand, we can create more strain on the native heart in the co-pulse mode when assessing the possibility of weaning from the LVAD in the recovery stage. Further studies are underway, including analyses of cardiac energy metabolism and myocardial perfusion using chronic heart failure models.

Conclusion

Based on our experimental results in goats with acute ischemic heart failure, LVAD can change MVO2. The MVO2 was reduced with the counter-pulse mode and increased with the co-pulse mode, relative to the continuous support mode, which we usually apply in clinical practice. This means that we can change the native heart load by controlling the LVAD rotation in synchrony with the cardiac rhythm. The changeable native heart load made by NHLCS may enhance the chance of BTR, especially for patients with ischemic heart diseases.

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