J Artif Organs (2009) 12:1–7
DOI 10.1007/s10047-009-0451-x

REVIEW

Journal of Artificial Organs Editorial Committee

Journal of Artificial Organs 2008: the year in review

Key words Artificial heart (basic) · Artificial heart (clinical) · Cardiopulmonary bypass · Artificial lung · Blood vessel prosthesis · Pacemaker · Artificial valve · Biomaterial · Tissue engineering · Dialysis · Apheresis · Artificial liver · Artificial pancreas · Artificial skin · Artificial muscle · Artificial bone · Artificial neuron

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 been also 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 Australia, Brazil, the Czech Republic, Germany, Korea, Poland, Singapore, Sweden, Taiwan, Turkey, the United Kingdom, the United States, and other countries have been accepted for publication, and the number of cited JAO articles in other journals has also been significantly increasing. In 2008, JAO was accepted for abstracting and indexing in the Web of Science/Citation Index Expanded, and the first (2010) Impact Factor will be available in 2011. Three years ago we started reviewing and summarizing all the articles published in the JAO in the previous year in order to provide an overview for our readers.[1–3] We have decided to continue this practice this year as well, and we have summarized below the articles published in Volume 11, 2008. Volume 11 of the JAO published 38 articles including 24

Received: February 16, 2009

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original papers, 7 review papers, 1 case report, 5 brief communications, and 1 obituary. These were related to the many aspects of the basic research, development, and clinical applications of artificial organs, and included articles on artificial heart, cardiopulmonary bypass, artificial lung, blood vessel prosthesis, artificial valves, dialysis, artificial kidney, biomaterials, tissue engineering, regeneration therapy, regulatory science, and other topics. We are pleased to present such excellent work in our journal. For Volume 11, we had a total of 52 reviewers who are specialists in the field of artificial organs. We offer our profound gratitude to those reviewers for their thoughtful reviews, critiques, and suggestions, which help our authors to improve the work they submit for publication.

Artificial heart (basic)

With regard to basic research on the artificial heart, we published four articles in total, including two original articles and two brief communications in 2008.

Y. Suzuki et al.[4] of Hirosaki University School of Medicine reported on the feasibility of BioMetal Helix (BMH) as an artificial muscle for dynamic cardiomyoplasty. BMH has been developed by the Toki Corporation and is an artificial muscle that is activated by an electric current. The fiber of BMH made from Ni-Ti alloy is a so-called shape memory alloy. The authors wrapped the soft bag of the simulated blood circuit using a BioMetal device made of eight BMHs. They measured the pressure inside the soft bag then the peak pressure was increased to 10 mmHg. The electrically controlled systolic phase lasted 1.5 s and the duration of the diastolic phase also lasted 1.5 s. They concluded that the artificial muscle may be potentially useful as a cardiac assist device. However, further work on the enhancement of the contraction and the speed of deformation are required.

A. Homma et al.[5] of the National Cardiovascular Center of Japan developed a compact wearable pneumatic driver that can drive the Toyobo diaphragm-type ventricular assist device (VAD) blood pump currently used widely in the Japanese clinical arena. The newly developed drive unit consists of a brushless DC motor, noncircular gears, a crankshaft, a cylinder-piston, and air pressure regulation valves. The size of the unit is 20 × 8.5 × 20 cm and it weighs 1.8 kg. As a performance evaluation test, they reported the maximum pump output was more than 7.0 l/min at 100 bpm against an afterload of 120 mmHg. Although the systolic ratio of this drive unit was fixed at 44%, the driving conditions were controlled at full–fill and full–eject conditions by regulating the beating rate and the driving pressure. Furthermore, they reported the results of long-term animal tests. Two calves were supported by the VAD which were driven by their wearable driver, and their durations of support were 30 and 39 days. In both cases, the calves remained in good condition until the termination of the experiments, and the mean bypass flow was maintained at more than 5.0 l/min. They concluded the newly developed pneumatic drive unit demonstrated sufficient ability to be used as a compact wearable drive unit for the Toyobo VAD blood pump.

Y. Abe et al.[6] of the University of Tokyo reported a nonpulsatile total artificial heart with 1/R control. Valveless undulation pump total artificial hearts (TAHs) were implanted in 18 goats, 4 of which goats survived for more than 1 month. Three weeks of long-term nonpulsatile TAH support could be tested in the goat that survived for 72 days. The general condition and organ function of the goat were not changed by the application of nonpulsatile mode. The sucking effect of the atria was very significant in nonpulsatile mode, resulting in hemolysis. Nonpulsatile TAHs under 1/R control are considered to be inadequate unless some pulsatility can be introduced to avoid a fatal sucking effect and to ensure sufficient inflow. A study of the TAH and its control is very valuable under current artificial heart circumstances as the ventricular assist devices are major topics in both the basic and clinical fields. Investigation of the total artificial heart should be continued to provide adequate new information for readers of the JAO.

T. Yamamoto et al.[7] of the Tokyo University of Science reported magnetic field immunity of the externally coupled transcutaneous energy transmission (TET) system for a totally implantable artificial heart. The immunity of the TET system to the magnetic field induced by an induction-heating (IH) cooker and the effect of a shield made with conductive tape with a slit to decrease the induced voltage were examined. The energy transformer was placed on the top plate of the IH cooker and induced voltage in transfer coils was measured. The shielding on the external coil reduced the induced voltage by 54%–76%. These basic studies of peripheral technologies for the artificial heart system are important to boost the system toward the clinical stage and should be studied further.

Artificial heart (clinical)

K. Sato et al.[8] of the Niigata University Graduate School of Medical and Dental Sciences reported the results of a frequency analysis of high-intensity transient signals (HITS) of transcranial Doppler ultrasound in patients supported with a Toyobo VAD. The significance of HITS of transcranial Doppler ultrasound remains unclear, but it may be related to microbubbles, microthrombus, bacterial mass, or some other entity. The authors evaluated HITS on seven VAD-supported patients before and during oxygen inhalation. Because the oxygen inhalation significantly decreased HITS, they speculated that HITS of VAD-supported patients may imply the presence of air microemboli.

Cardiopulmonary bypass

With regard to basic and clinical research on cardiopulmonary bypass (CPB), we published three original articles and one brief communication in 2007.

R. Kansaku et al.[9] of Juntendo University, the National Cardiovascular Center, and the Terumo Corporation evalu-

ated the combined therapy of diluted CPB and liposome-encapsulated hemoglobin (LEH) focusing on the influence of LEH on oxygen metabolism. Male kid goats ($n = 8$) were divided into two groups: LEH and control. CPB was maintained at 36°–37°C. There was no significant difference in hemoglobin concentration after initiation of CPB, and no distinction in oxygen delivery between the two groups (11.0 ± 2.0 ml/kg/min in the LEH group and 11.0 ± 2.3 ml/kg/min in the control group). Oxygen consumption in the LEH group (2.5–2.7 ml/kg/min), however, had a tendency to be higher than that in the control group (2.4–2.5 ml/kg/min). In addition, the lactate/pyruvate ratio decreased earlier in the LEH group. The authors concluded that the application of LEH in the pump-priming solution improved decreased aerobic oxygen metabolism during CPB without any serious adverse effects.

Y. Suzuki et al.[10] of Hirosaki University investigated the efficacy of poly-2-methoxyethylacrylate (PMEA) coating for CPB circuits. Eleven pediatric ventricular septal defect patients were divided into group C (no coating, $n = 5$) and group P (PMEA coating, $n = 6$). Elevation of thrombin–antithrombin complex and neutrophil elastase was suppressed in group P ($P < 0.05$). Observation of the artificial lung surface using an electron microscope clearly revealed that fewer blood cells were adherent to the surface in group P. Fibrinogen level and postoperative bleeding were relatively lower in group P. The platelet count and β-thromboglobulin level were the same in both groups. The authors concluded that the PMEA-coated circuit reduced activation of the coagulation system and the inflammatory reaction in pediatric cardiac surgery.

Y. Tomizawa et al.[11] of Tokyo Women's Medical University, and co-authors from Hiroshima International University, Jichi Medical University, and Keio University assessed the performance of hand cranking of a roller pump quantitatively by an objective method using the ECCSIM-Lite educational simulator system. A roller pump connected to an extracorporeal circuit with an oxygenator and with gravity venous drainage was used. In a perfusion seminar, 1-min hand-cranking drills were conducted by volunteers using this system according to a prepared scenario. The results showed that good performance was not related to the clinical experiences, while manipulating the venous return clamp required practice. The authors concluded that it is beneficial for perfusionists and patients to include hand-cranking practice in periodic extracorporeal circulation crisis-management drills, although the necessity of performing hand cranking during perfusion due to pump failure is rare.

T. Yamane et al.[12] of the National Institute of Advanced Industrial Science and Technology, reported pivot wear of a centrifugal pump supported by a passive magnetic bearing. The pivot durability regarding the combination of male–female pivot radii was examined through rotating wear tests and animal tests. A combination of different radii for the male–female pivots indicated a wear rate of 4.38–5.29 μm/day in wear tests. A combination of similar radii for the male–female pivots showed a wear rate of 0.67 μm/day in wear tests and a wear rate of 2.1 μm/day in animal tests.

Blood vessel prosthesis

M. Shiono[13] from Nihon University Itabashi Hospital, Tokyo, reported a surgical result for acute type A aortic dissection using gelatin-resorcin-formalin (GRF) glue. When emergency cases were operated on, their hospital mortality rate was as low as 6.7% and the actuarial survival rate was 81.5% after 5 years and 54.8% after 10 years. With GRF glue, excellent tissue adhesion and hemostasis capabilities on the operating table have been reported, and cytotoxicity and tissue necrosis could be the cause of long-term complications such as re-dissection and false aneurysms.

C.L. Bara and J.F. Verhey[14] from the Hannover Medical School, Hannover, Germany, evaluated the supposed benefit of a prosthesis incorporating the natural geometry of the sinuses of Valsalva. The flow and pressure distributions were examined, and it was found that the sinus design only slightly increased the mean pressures and the velocities in both the ascending aorta and in the coronary arteries in their model. In a previous study, it was suggested that the coronary flow pattern may be affected by the presence of sinus; and if that were the actual case, it was difficult to evaluate the difference with this current study design.

Artificial valve

With regard to basic and clinical research on the artificial valve, we published one review paper, five original articles, and one brief communication in the journal.

H.S. Lee et al. from the National Cardiovascular Center continued to investigate mechanical heart valve (MHV) cavitation in a ventricular assist device (VAD). In 2007 they reported formation of cavitation bubbles associated with the Medtronic Hall valve (M-H valve) in a pneumatic VAD.[15] They evaluated formation of cavitation bubbles associated with the Sorin Bicarbon bileaflet valve (S-B valve) in comparison with the M-H valve in 2008.[16] The valve-closing velocity, visual cavitation time, and root mean square (RMS) pressure of the M-H valves were greater than those with of the S-B valve. They concluded that both the visual cavitation time and RMS pressure presented the cavitation intensity, and that this was an important factor when estimating mechanical heart valve cavitation intensity in an artificial heart.

It is useful for follow-up of patients after prosthetic valve replacement to develop a new noninvasive and sensitive diagnostic method of detecting valve malfunction. H. Sugiki et al.[17] from the Hokkaido University School of Medicine reported that the continuous wavelet transform (CWT) using the modified Morlet wavelet (Morlet CWT) is an effective tool for detecting the split interval (SI) of its closing sound of normally functioning bileaflet valves (NBVs) in 2007. In 2008 they evaluated the clinical significance of this split interval of malfunctioning bileaflet valves (MBVs).[18] They analyzed 218 valves in 184 patients, including normal monoleaflet valves ($n = 10$), NBVS ($n = 198$),

and MBVs ($n = 10$). The CWT of monoleaflet valves showed a single spike, whereas NBVs exhibited a clear split. The split was not found in six of ten patients with MBVs. The other four patients had a distinct split, but the coefficient of variation of valve SI was significantly lower for MBVs than for NBVs. They concluded that the signal analysis method using the Morlet CWT could be a useful tool to screen the function of bileaflet valves.

T. Akutsu et al. from Kanto Gakuin University reported two interesting in vitro experimental studies of bileaflet mechanical valves concerned with valve-closing sounds in the mitral position and the turbulent flow field in the aortic position. In the first study,[19] four bileaflet prostheses – the St. Jude Medical (SJM) valve, the On-X valve with straight leaflets, the Jyros (JR) valve, and the Edwards MIRA (MIRA) valve with curved leaflets – were tested in the pulsatile flow facility to estimate the corresponding three-dimensional flow field and valve-closing sounds using Morlet CWT. The SJM, the On-X, and the MIRA valves generated a centrally downward circulation that opposed the valve leaflet closing movement and resulted in relatively loud valve-closing sounds and a split in valve-closing sounds. On the other hand, the JR valve, which generated a peripherally downward circulation, showed the lowest sound level and no split of closing sounds. They concluded that the difference in overall flow circulation seemed to affect the closing behavior of the valve leaflets and resulting valve-closing sounds.

In the second study,[20] three bileaflet prostheses – the SJM valve, the On-X valve (with straight leaflets), and the MIRA valve (with curved leaflets) – were tested inside a simulated aorta under pulsatile flow conditions to analyze the aortic flow field resulting from the different valve designs using particle image velocimetry. The two new valves, the On-X and the MIRA valves, opened more quickly than the SJM valve and provided a wider opening area. The flow through the central orifice of the SJM valve had a low velocity compared with that of the newer designs; the newer designs had a strong flow through all orifices. The On-X valve generated a simple jet-type flow, whereas the MIRA valve (with circumferentially curved leaflets) generated a strong but three-dimensionally diffuse flow, resulting in a more complex flow field downstream of the aorta. The clinically more adapted 180° orientation provided a less diffuse flow than 90° orientation did. They concluded that the small differences in leaflet design in the bileaflet valves generated noticeable differences in the aortic flow; the newer valves showed strong flows through all orifices.

S. Tokunaga and R. Tominaga[21] extensively reviewed the current status of artificial valves in Japan. On valve selection for the aortic position, the number of tissue valves used exceeded that of the mechanical valves in 2005 for the first time in Japan. For surgery of the mitral valve, there is a tendency toward valve repair rather than valve replacement. In fact, the number of mitral valve repairs increased from 1237 in 2000 to 2315 in 2005, and that of mitral valve replacements decreased from 2048 to 1069 in the same period. For selection of the prosthetic valve, the use of a bioprosthesis is increasing just as for the aortic position, although, unlike the case with the aortic position, more patients received mechanical valves (1402) than received bioprostheses (567) in 2005 in Japan. However, the percentage of tissue valves used has also been increasing (16.7% in 2000 and 28.8% in 2005).

Y. Sakamoto and his co-workers studied patient–prosthesis mismatch after aortic valve replacement using a bioprosthesis.[22] Based upon the residual transvalvular pressure gradient, they concluded that an indexed effective orifice area of less than 1.25 cm^2/m^2 might be considered the threshold for patient–prosthesis mismatch in patients with a stented bioprosthesis. In their results, most patients showed improvement in postoperative left ventricular mass regardless of the degree of residual pressure gradients. Thus, further studies would be necessary to test their results.

S. Tokunaga and his colleagues published an interesting paper on the selection of a prosthetic valve for isolated pulmonary valve replacement.[23] Because the mechanical valve had a higher incidence of thrombosed valve, they concluded that a bioprosthesis is recommended for pulmonary valve replacement if a homograft is not available.

Biomaterial

In 2008 we had two review articles and one original article about biomaterials in the journal, each of which provided us with important information.

Metallic biomaterials have been used mainly for the fabrication of medical devices for the replacement of hard tissue, such as artificial hip joints, bone plates, and dental implants, owing to the mechanical performance of metals. Nowadays, biofunctionality of metallic biomaterials by fusing and harmonizing them with ceramics, polymers, or both, has become the trend of metallic biomaterial research. Dr. M. Niinomi from Tohoku University, Sendai, has described this trend in recent research and the development of metallic biomaterials, including stainless steel, cobalt alloys, and titanium alloys.[24]

Of course, polymeric biomaterials are another important materials candidate for artificial organs. Polymeric membranes especially have been a major concern of researchers for developing artificial kidney, artificial lung, and artificial heart housing and diaphragm. Dr. H. Kawakami from Tokyo Metropolitan University, Tokyo, conducted a review of polymeric membranes for artificial organs.[25] Dr. Kawakami argued that the development of synthesized polymeric membrane materials for artificial organs based on well-defined designs is essential. Furthermore, the innovations represented by nanotechnology in recent years have had a great impact on the field of artificial organs. Precise nano-processing of a material surface, nanocoating, nanopatterns, and self-assembled nanomaterials, among others, may be utilized in the design of materials and synthesized at the atomic and molecular level for use in artificial organs.

Another concern of biomaterials is safety, and the method of evaluation is one of the key factors for determining the safety of biomaterials. Dr. B. Hexig et al. from the National Institute of Health Sciences, Tokyo, Japan, describe the cytotoxicity of three kinds of commercially

available absorbable hemostats.[26] Their report of the investigation of the correlation between the cytotoxicity and the extraction period of surgical materials is helpful for predicting the effect of prolonged in vivo use of biomaterials on surrounding cells, tissues, and organs.

Tissue engineering

In 2008, we had three articles in the field of tissue engineering. Two papers addressed cardiac tissue engineering, and one paper was related to a tissue-engineered vascular graft.

"Cell sheet engineering," proposed by Prof. Okano et al., is a unique technology to construct tissues by layering cell sheets obtained using temperature-responsive culture dishes. The efficacy of cell sheet engineering has been demonstrated not only in basic research but also in clinical treatments. In cardiac tissue engineering, construction of 3-dimensional tissues having sufficient microvessels is a key issue in engineering powerfully contractile myocardium. H. Kobayashi et al. from Tokyo Women's Medical University developed cytokine-secreting cell sheets.[27] They sandwiched peripheral blood endothelial progenitor cells (EPCs) between subcutaneous tissue-derived fibroblast sheets and transplanted the constructs onto ischemic rat hearts. The data showed that the sheets improved damaged heart function with inhibition of fibrotic tissue formation and acceleration of neovascularization. Moreover, co-cultured EPCs participated in new blood vessel formation. These data suggested that co-cultured cell sheet transplantation was more effective than either cell sheet transplantation alone or EPC injection.

One reason for the weak contractile force of engineered cardiac tissues may be due to the differences of mRNA expressions in in vivo and cultured cells. T. Nakamura et al. from Yamagata University investigated the mRNA expressions of four transcriptional factors related to cardiomyocyte differentiation: serum response factor (SRF), myocardin, Nkx2.5, and p300; and two major proteins constituting cardiac intercalated disk, N-cadherin and connexin43, under in vivo and culture conditions.[28] They suggested that myocardin was a proper candidate for a gene transfection strategy to enhance engineered cardiac tissue, because myocardin was expressed at a lower level in cultured cells than in in vivo cells. Moreover, they partly explained the reason for the weak contractile force of engineered cardiac tissue based on the data showing that the mRNA expressions of N-cadherin and connexin43 in culture were lower than those in vivo.

Owing to the lack of anti-thrombogenicity in small-diameter vascular grafts, there are great expectations for the development of tissue-engineered arteries. Y. Narita et al. from the Nagoya University School of Medicine, developed decellularized small-diameter grafts from canine ureters.[29] They reported that the degree of decellularization and the maintenance of the matrix were best in the treatment with Triton-X 100 among four different chemical agents: Triton-X 100, deoxycholate, trypsin, or sodium dodecyl sulfate. Implantation in canine carotid arteries showed that the decellularized ureters pre-seeded with endothelial cells and myofibroblasts were patent for 6 months after the operation, whereas the non-seeded decellularized ureters and Polytetrafluoroethylene (PTFE) grafts became occluded within a week. They concluded that further studies, such as improvement of incomplete decellularization and establishment of a method for reconstruction of a smooth muscle layer, are necessary to guarantee the safety of the tissue-engineered grafts.

Dialysis

With regard to dialysis, we published three original articles and one brief communication in 2008.

M. Matsuda et al.[30] of Himeji Dokkyo University evaluated changes in the characteristics of membrane surfaces due to shear stress and internal filtration in in vitro dialysis tests using blood substitutes. Elution of polyvinyl-pyrrolidone (PVP) from the polyester–polymer alloy (PEPA) and the polysulfone (PS) membranes were evaluated during a 4-h dialysis. PVP on the PEPA membrane was eluted by both shear stress and internal filtration, whereas that on the PS membrane was eluted only by internal filtration. PVP retention on the PEPA membrane decreased with increasing shear stress as well as shear-stress loading time. The root-mean-square roughness, an indicator of surface roughness, of the PEPA membrane surface decreased due to elution of PVP.

A.B. Libório et al.[31] of the University of São Paulo, Brazil, performed a cross-sectional study to identify and quantify each component of acidosis in hemodialysis maintenance patients. Sixty-four hemodialysis maintenance patients and 14 controls were enrolled in the study. Gasometrical and biochemical analysis were performed before the midweek dialysis session. Quantitative physicochemical analysis was carried out using Stewart methodology. As a result, hemodialysis patients were found to have mild acidemia secondary to metabolic acidosis. The metabolic acidosis was due to retention of unmeasured anions, hyperchloremia, and hyperphosphatemia. The unmeasured anions and hyperchloremia had a similar acidifying effect, corresponding to almost 90% of the metabolic acidosis. The authors concluded that unmeasured anions and hyperchloremia, in addition to phosphorus, were important components of acidosis in hemodialysis maintenance.

K. Nishimura et al.[32] of Mie University, in their brief communication, looked into why the 7.5% icodextrin solution, a solution in clinical use for peritoneal dialysis, has a broad distribution of molecular weights. Icodextrin, a mixture of polysaccharides of α-(1→4) polyglucopyranose having 10% branched chains, has distinguishable water transport characteristics as compared with those of conventional d-glucose owing to a wide distribution of molecular weights. The results of this study suggested that fractions in the molecular range between 8.3 and 19.3 kDa, where the distribution profile was less influenced by enzymatic degradation as well as relatively prolonged retention, preferably contributed to water transport as a result of maintaining an oncotic pressure gradient.

A. Takezawa et al.[33] of the Shonan Institute of Technology examined the ultrafiltration characteristics of a commercial dialyzer by measuring the sieving coefficient for three proteins (cytochrome c, chymotrypsinogen, and albumin) in a bovine blood system, which was compared with that in aqueous solution. They found that the ultrafiltration of cytochrome c and chymotrypsinogen was reduced by the masking effect of erythrocytes. The sieving coefficient for albumin in bovine blood was almost the same as that in the aqueous solution when only albumin was added, whereas that in bovine blood was steadily higher than that in the aqueous solution when all three proteins were added. The authors concluded that this phenomenon was probably caused by the stirring effect of erythrocytes that would disturb the concentration polarization of albumin formed near the membrane.

Artificial skin, muscle, bone, and neuron

Retinal prostheses are promising treatment modalities for retinal outer-layer degeneration such as retinitis pigmentosa. T. Tamaki et al.[34] developed polyethylene films coupled with photoelectric dye molecules, 2-[2-[4-(dibutylamino)phenyl]ethenyl]-3-carboxymethylbenzothiazolium bromide, which convert photon energy to electrical potentials. To assess biological safety, this material was implanted in the subretinal space of normal adult rats. Glial fibrillar acidic protein up-regulation was found at one month implantation for both the plain film and the dye-coupled recrystalized film without any tissue damage.

An article by K. Okamoto et al.[35] also reports on the biological safety of photoelectric dye-based retinal prostheses as mentioned in T. Tamaki et al.[34] In this safety assessment they used retinal cells derived from neurosensory retinas at the 12-day embryonic stage. This photoelectric dye showed no cytotoxicity to chick retinal cells or retinal pigment epithelial cells on short-term exposure (2 to 4 days) accompanied with some protective effects.

N. Yamada et al.[36] evaluated the efficacy of allogeneic cultured dermal substitute (CDS) on wound healing in six patients with intractable skin ulcers on the lower extremities. They reported a marked decrease of the wound area, 9%–25% of the original size, within 6 weeks associated with re-epithelialization. Based on this clinical outcome it is suggested that allogeneic CDS is a safe and powerful tool for the treatment of intractable skin ulcers.

Three original articles on allogeneic cultured dermal substitute (CDS) have been published by a group at Kitasato University. A. Hashimoto and Y. Kuroyanagi[37] reported the mass production of CDS from donated skin. Fibroblasts were isolated and proliferated over nine successive cultivations. CDS was prepared by plating cultured fibroblasts on a two-layered spongy matrix of hyaluronic acid and atelocollagen, followed by culturing for 1 week. In total, 47 sheets of CDS measuring 10 × 10 cm were prepared. The density of fibroblasts and the levels of vascular endothelial growth factor, basic fibroblast growth factor, hepatocyte growth factor, transforming growth factor-β1, and interleukin-8 (all of which are relatively constant for each cultivation cycle) were monitored. It is calculated that about 1000 sheets of CDS measuring 10 × 10 cm with relatively standard characteristics can be prepared using all the working cells prepared from a piece of donated skin measuring 1 × 1 cm.

N. Yamada et al.[38] reported re-epithelialization of CDS cryopreserved at −152°C and compared it with that of fresh samples in a clinical study. The re-epithelialization time for the cryopreserved and fresh CDSs was 8.21 ± 1.4 and 8.21 ± 1.3, respectively, which revealed that this cryopreservation method is applicable for clinical use.

N. Kurokawa et al.[39] of Osaka Medical College reported the application of CDS for amelioration of maxillary bone growth suppression after cleft plate operations in rats. Rat CDSs were prepared in a similar manner and placed at the site of removed periosteum. It was found that CDS promotes wound healing and reduces scar formation and thereby ameliorates indirectly the growth of maxillary bone.

H. Saijo et al.[40] reviewed the clinical application of artificial bone in the maxillofacial region. The design and volume of the artificial bone for implantation were determined by using a reconstructed 3-D model created from Digital Imaging and Communications in Medicine (DICOM) data of computed tomography (CT) images. A computer-aided design (CAD) model was created. A combination of Apaceram (hydroxyapatite) and Biopex-R (calcium phosphate paste) was used in a clinical case. Biopex-R (α-TCP), which consists of a powder and a malaxation liquid and which becomes a paste upon mixing and hardens by hydration, was revealed to be useful in extraction cavities and for the binding of small spaces between the bone and the Apaceram.

Others

K. Fukamachi[41] from the Cleveland Clinic, Cleveland, Ohio, reviewed new devices for the treatment of functional mitral regurgitation. Three categorized groups of devices, annuloplasty, edge-to-edge repair, and ventricular reshaping, were introduced in this review. They could be placed percutaneously or minimally invasively without cardiopulmonary bypass. Many of the devices are now in clinical trials. Outcomes equal to or better than surgical repairs are expected to be achieved. This author focused on the ventricular reshaping techniques after he conducted some studies. There are numerous issues that need to be addressed before those techniques become standard therapy, however.

S. Takatani[42] of Tokyo Medical and Dental University contributed an obituary and delivered a eulogy for Dr. Tetsuzo Akutsu, who passed away on August 9, 2007. Dr. Akutsu started artificial heart research in 1957 at the Cleveland Clinic, where he reported the world's first survival of a dog for 1.5 hours with a man-made prosthetic heart. Since then, he had followed his dream of perfecting the artificial heart for over 50 years, at New York Maimonides Memorial Hospital, the University of Mississippi, the Texas Heart

Institute, the National Cardiovascular Center, Tokyo Women's Medical College, Terumo Corporation, and Tokyo Medical and Dental University. He was truly a pioneer in the field of artificial heart research that became the basis for advancing various treatment technologies for end-stage heart failure. In that sense, we are all indebted to Dr. Akutsu's life-long engagement in artificial heart research. We will long remember his great contribution to the field of artificial organs.

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Gen Thorac Cardiovasc Surg (2010) 58:25–29
DOI 10.1007/s11748-009-0482-5

CASE REPORT

Bilateral lung transplantation with closure of ventricular septal defect in a patient with Eisenmenger syndrome

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Received: 24 January 2009 / Accepted: 6 April 2009

Abstract We report the first case with Eisenmenger syndrome secondary to an isolated perimembranous ventricular septal defect (VSD) in a patient who underwent bilateral lung transplantation and closure of the VSD in Japan. This male patient was diagnosed as having a VSD associated with severe pulmonary hypertension at the age of 7, and right unilateral pulmonary artery banding was performed at age 9. At 38 years of age, we performed bilateral cadaveric lung transplantation with patch closure of the VSD. Explant pathology revealed grade 3 for the right lung and grade 4 for the left lung by the Heath-Edwards classification. The ventricular contractility had gradually improved, and ventricular arrhythmia requiring amiodarone prior to lung transplantation had disappeared. When cardiac function is preserved, bilateral lung transplantation is an option for patients with Eisenmenger syndrome secondary to VSD and should be considered as an alternative to heart–lung transplantation, especially in Japan, where donor organ shortage is critical.

Key words Lung transplantation · Eisenmenger syndrome · Ventricular septal defect (VSD)

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Introduction

The outcome of lung transplantation for Eisenmenger syndrome is reported to be poor, as the International Society of Heart and Lung Transplantation (ISHLT) Registry 2007 noted that 30-day survival and median survival time after lung transplantation for patients with Eisenmenger syndrome associated with ventricular septal defect (VSD) are 72% and 1 year, respectively. Herein, we report the first case in Japan of Eisenmenger syndrome with VSD treated with bilateral lung transplantation and closure of the VSD.

Case

A male patient with dyspnea on effort and cyanosis was diagnosed as having VSD and severe pulmonary hypertension (PH) at the age of 7. He underwent right unilateral pulmonary artery (PA) banding at the age of 9 to evaluate reversibility of PH and to protect the right lung. Although his symptoms had been tolerable, dyspnea on effort gradually progressed; and he had massive hemoptysis at 21 years of age. Home oxygenation therapy was introduced at the age of 30 years.

At the time of registration for the lung transplantation, the clinical cardiac and respiratory functional status was New York Heart Association (NYHA) III and Hugh-Johns (HJ) IV. Cyanosis, hepatomegaly, and clubbed fingers were noted by physical examination. The cardiac catheter examination showed Eisenmenger syndrome with step-down of SaO_2 (left ventricle 91.7% and aorta 85.6%) and severe PH: 108/54 (76) mmHg and 30 Wood units in the pulmonary vascular resistance index

(PVRI). The Qp/Qs ratio increased from 1.06 to 1.75, and the Rp/Rs ratio decreased from 0.86 to 0.50 by 5 l of O_2 inhalation; the PVRI did not normalize. Nitric oxide or epoprostenol did not affect the PVRI. The left ventricular (LVEF) and right ventricular (RVEF) ejection fractions and cardiac index (CI) were 46.5%, 51.6%, and 2.2 l/min/m^2, respectively.

Ultrasonographic cardiography (UCG) revealed perimembranous VSD (35 mm in diameter) with bidirectional shunt and no right ventricle outflow tract obstruction. Thus, the cardiac function was relatively preserved and the functional recovery was expected after VSD closure if the after-load caused by pulmonary vascular resistance was released by bilateral single lung transplantation. A Holter electrocardiogram showed coupled ventricular premature conduction (VPC) and 77 VPCs (Lown IVa), and the patient was prescribed mexiletine hydrochloride. As VPCs increased and the left ventricle gradually dilated with a decrease in the LVEF, mexiletine was converted to amiodarone. Blood analysis showed hemolytic bilirubinemia (total bilirubin 5.3 mg/dl) caused by plethora (hemoglobin 21.6 g/dl), whereas liver and renal function was preserved.

After discussions about the operative procedure—bilateral lung transplantation or heart-lung transplantation (HLT)—taking these data into consideration, we decided to perform bilateral lung transplantation with VSD closure. We considered that the ventricular dysfunction would be reversible after the lung transplantation. The consensus for bilateral lung transplantation for this patient was obtained at the Kinki Lung Transplantation Conference in January 2001, and the patient was registered on the waiting list for lung transplantation after the approval of the Central Assessment Committee for Lung Transplantation in Japan in June 2001.

Pretransplant UCG revealed a large membranous VSD measuring 35 × 21 mm in diameter with blood flow of 0.8 m/s, right ventricular (RV) hypertrophy, nearly systemic PH, and 52% LVEF. Chest radiography revealed postbanding dilatation of the right main pulmonary artery (PA) (Fig. 1). Arterial blood gas (ABG) analysis showed pH 7.426, PaO_2 43.2 mmHg, and $PaCO_2$ 32.1 mmHg at room air.

The brain dead donor was a man in his fifties who had suffered a cerebral vascular disorder. The predicted vital capacity (VC) size match of donor to recipient was 85%, and HLA typing was two mismatches.

Bilateral cadaveric lung transplantation with a patch closure of the VSD was performed in December 2007 when the patient was 38 years old. The operating time was 14 h 20 min, and the total volume of blood loss was 3580 ml; the cardiopulmonary bypass (CPB) time was 7 h 55 min, and the aortic cross-clamp time was 49 min.

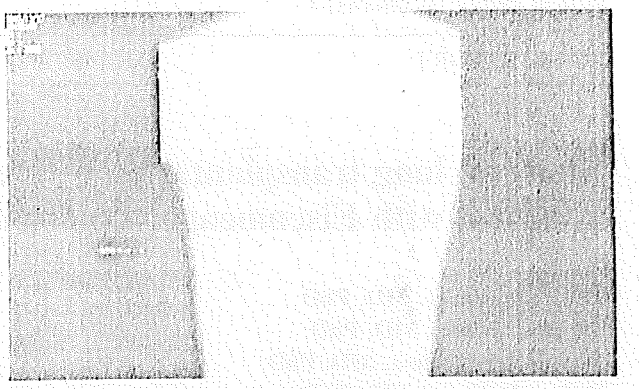

Fig. 1 Chest radiograph before lung transplantation. Postbanding dilatation of the right main pulmonary artery was found at the right hilum

A clamshell incision through the fourth intercostal space with additional caudal median sternotomy was made for a better view of the vena cava and VDS exposure. VSD closure was initially carried out. After the bicaval CPB was established, the ascending aorta was clamped and cardiac arrest was induced by cold blood cardioplegia. VSD was closed via the right atrium with a 0.4-mm expanded polytetrafluoroethylene (ePTFE) patch that measured 40 mm in diameter using a 4-0 polypropylene continuous suture. Then, bilateral lungs were removed and the grafts were anastomosed in the order: left bronchus, left pulmonary vein (PV), left PA, right bronchus, right PV, and right PA. Continuous sutures for the membranous site and interrupted sutures for the cartridge site were applied for the bronchial anastomosis using 4-0 polydioxanone. Using 5-0 polypropylene continuous sutures, the right PA was anastomosed between the superior vena cava and ascending aorta, which was on the proximal side of the previous PA banding procedure. ABG analysis performed just after reperfusion showed PaO_2 96.8 mmHg, $PaCO_2$ 39.4 mmHg, and FiO_2 60%.

Histopathologically, the explanted lungs showed stenotic pulmonary arterioles with laminar intimal fibrosis. By the Heath-Edwards classification, the right lung, which had been treated with PA banding, had grade 3 histological alteration, and the left lung had grade 4 (Fig. 2). Although a plexiform lesion was not found, several arterioles showed irreversible obliterative change.

The tracheal tube was extubated on postoperative day (POD) 4 after improvement from reperfusion injury. However, reintubation followed by mechanical ventilation was required due to aspiration pneumonia, which was caused by bilateral recurrent nerve palsy and left phrenic nerve palsy. Mechanical ventilation was discontinued on POD 28 with a tracheostomy and physical

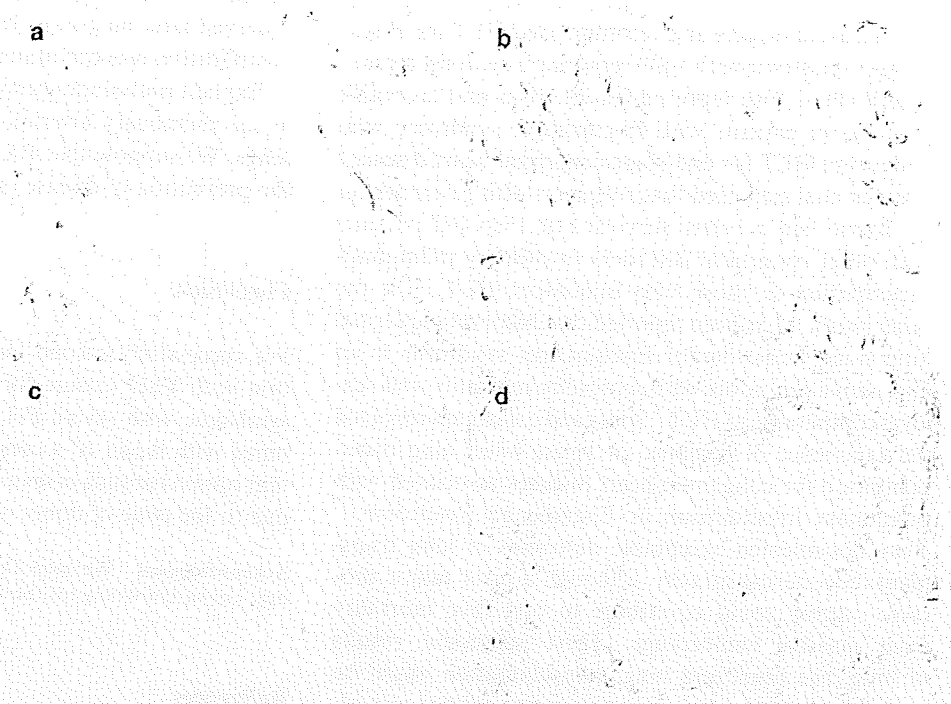

Fig. 2 Explant pathology. **a**, **b** Microscopic findings in the right lung by hematoxylin-eosin (H&E) (**a**) and elastica van Gieson (EVG) (**b**) staining. The right lung, which had been treated with pulmonary artery (PA) banding, was grade 3 by the Heath-Edwards classification. Laminar intimal fibrosis was found. (**c**) H&E and (**d**) EVG staining for the left lung. Several arterioles show irreversible obliterative change. The histological diagnosis was grade 4

rehabilitation. The tracheostomy was closed on POD 80 following recovery of recurrent and phrenic nerve function. Immunosuppressive treatment had been performed with cyclosporine, mycophenolate mofetil, and steroid. The patient had no episode of rejection during the postoperative course, although cytomegaloantigenemia had continued for a month, which had been treated with ganciclovir followed by foscarnet.

Four months after transplantation, a pneumothorax on the right side developed during a routine bronchoscopy examination; thus video-assisted thoracoscopic (VATS) ligation of an apical ruptured bulla was performed. The status of the patient 6 months after transplantation was NYHA II and HJ II; and ABG assays showed PaO_2 105 mmHg, $PaCO_2$ 35.7 mmHg, and pH 7.420 under room air. Chest radiography showed clear lung fields with the remodeling of the RV enlargement (Fig. 3). Gradual improvement of LV contraction was shown by UCG (ejection fraction 54%, fractional shortening 28%), though the RV hypertrophy remained and brain natriuretic peptide (BNP) had a sustained high level (445 pg/dl at 7 month, 314 pg/dl at 10 month). Ventricular arrhythmia has disappeared without medication. Transient RV outflow tract (RVOT) narrowing (4 mm at systolic phase, 1.5 m/s of flow) detected with UCG 6 months postoperatively has improved without medication. The patient was discharged 10 months after the transplantation and performs without any assistance.

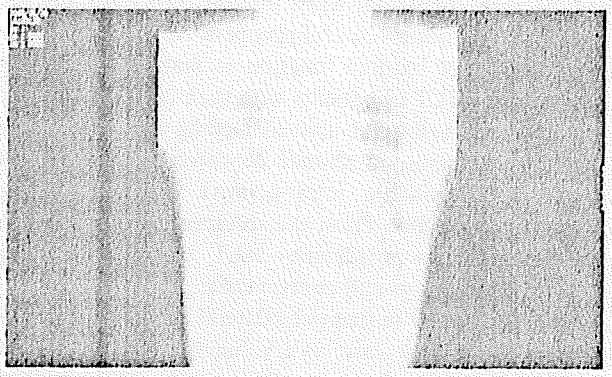

Fig. 3 Chest radiograph 6 months after lung transplantation. The graft is fitted to the thorax of the recipient. Right ventricular enlargement is diminished compared to that on the preoperative chest radiograph

Discussion

The former registry data from ISHLT summarized by Waddell et al. indicated the survival benefit of HLT for patients with Eisenmenger syndrome secondary to VSD.[1] Although the superior outcome of HLT for Eisenmenger syndrome to VSD was reported as compared with that to atrial septal defect (ASD) or patent ductus arteriosus (PDA), they could not identify the medical reason.[1] They, however, pointed out the possibility of the differ-

ence of physiological derangement between pre- and posttricuspid defects and recommended HLT for Eisenmenger syndrome with VSD requiring a complex repair.[1] Goerler et al. also reported feasible risks and favorable outcome in patients with Eisenmenger syndrome who underwent HLT for end-stage congenital heart disease.[2] Trulock et al. reported that recipients with Eisenmenger syndrome had a better survival rate than did patients with other congenital disorders or primary pulmonary hypertension in those who underwent HLT.[3] On the other hand, it has been reported that bilateral sequential lung transplantation for Eisenmenger syndrome is an alternative procedure with morbidity/mortality and survival comparable to HLT.[4] Spray and colleagues reported the experience of pediatric or young adult lung transplantation for congenital heart diseases associated with pulmonary hypertension or Eisenmenger syndrome.[5–7] They documented acceptable outcomes of lung transplantation during infancy, although a prior major thoracic surgery could contribute to operative mortality from massive hemorrhage. These successful results of lung, not heart and lung, transplantation might be caused by the potential of postoperative cardiac remodeling in children or young adults. The present case could imply that lung transplantation is indicated in some adults with congenital heart disease with Eisenmenger syndrome, although careful preoperative evaluation for reversibility of cardiac function is mandatory. When considering HLT in patients with such congenital heart diseases, the collateral arterial feeding from the chest wall or mediastinum should be carefully assessed to avoid uncontrollable intraoperative bleeding during surgery using CPB. Thus, the recommended procedure for Eisenmenger syndrome—HLT or bilateral lung transplantation—is still controversial.

We performed sequential bilateral lung transplantation in the present case, as LV function was preserved and improvement after transplant was expected; another reason was the social issue of donor shortage and organ sharing in Japan. That is, the donor heart could be transplanted to another cardiac recipient, which is also mentioned as a reason to indicate lung transplantation for patients with Eisenmenger syndrome.[2] RVOT obstruction after lung transplantation for Eisenmenger syndrome was previously reported as a potentially fatal postoperative complication.[8] HLT could have avoided such risk, although the operative mortality is still high due to various complications during the perioperative period. In the present case, transient RVOT narrowing was observed after lung transplantation, although no severe complication was encountered during the operation.

Explant pathology showed the histological difference in the pulmonary arterioles between the right and left lungs. We suppose that PA banding could contribute to the prevention of disease progression on the right lung.

Conclusion

We successfully carried out bilateral lung transplantation with VSD closure for a patient with Eisenmenger syndrome with severe PH. Lung transplantation combined with repair of a congenital anomaly is an important option for such cases with preserved cardiac function due to the issue of donor shortage in Japan.

Acknowledgment We thank Dr. E. Morii, Department of Pathology, Osaka University for the histopathological diagnosis.

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Invited commentary

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I read this case report by Inoue et al. with great interest. Increased understanding and awareness of congenital heart disease has allowed early identification of these children; and advances in surgical techniques, anesthesia, and medical treatment have rendered most forms of congenital heart disease treatable. However, some patients with congenital heart disease develop Eisenmenger syndrome, for which heart–lung or lung transplantation remain the treatment of last resort. There are three transplant options for Eisenmenger syndrome: single lung transplantation (SLT), bilateral lung transplantation (BLT), and heart–lung transplantation (HLT). Cardiac repair with BLT appears to have a better postoperative course than SLT but carries potential morbidity associated with longer cardiopulmonary bypass. HLT is a simpler operation than BLT with repair of congenital heart disease but requires allocation of two organs from the scarce donor organ supply. It also adds the risk of cardiac graft coronary vasculopathy and is less tolerant of the ischemia time.

Although Waddell et al.[1] suggested that HLT appears to offer a survival benefit for Eisenmenger syndrome secondary to ventricular septal defect and should be considered the operation choice, the best option for this particular patient should be determined not only by the medical data but also by the social issue. Considering the current status of severe donor shortage in Japan, HLT should be offered only to patients who have no other choice.

Bilateral lung transplantation and closure of the ventricular septal defect in this particular case would be challenging because of the prior right pulmonary artery banding. The history of right thoracotomy would result in a certain degree of pleural adhesion and increased collateral circulation through bronchial arteries. The right pulmonary artery anastomosis was carried out between the superior vena cava and the ascending aorta. The difficulties were well reflected by the long cardiopulmonary bypass time (7 h 55 min) and large blood loss (3580 ml). Luckily, the prior thoracotomy was on the right side in this case. I assume the authors could take down the adhesions before hemarginizing the pat[illegible] I personally had a nightmare experience in BLT and closure of a patent ductus arteriosus in a middle-aged woman who had had a prior left thoractomy for open lung biopsy. A tight pleural adhesion was found behind the heart, which had to be taken down under cardiopulmonary bypass. As a result, uncontrollable bleeding was encountered.

The Osaka transplant group has been a leading institution of Japanese thoracic organ transplantation. They performed the first successful heat transplantation in 1999, cadaveric lung transplantation in 2000, and heart–lung transplantation in 2009. I congratulate authors for achieving another triumph.

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International Journal of Cardiology xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Letter to the Editor

Novel software package for quantifying local circumferential myocardial stress ☆

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ARTICLE INFO

Article history:
Received 8 May 2009
Accepted 12 May 2009
Available online xxxx

Keywords:
Wall stress
Janz
Cardiac function
Preload
Afterload

ABSTRACT

Local myocardial stress is an important index of ventricular loading conditions. We developed a novel software package to provide estimation of local circumferential stress in the entire left ventricle (LV) based on Janz's method using contemporary LV imaging techniques. The aim of this study was to confirm the validity of our novel software by comparing local circumferential stress (local σ) with global equatorial stress (global σ) values. We acquired 30° right anterior oblique LVG images in 74 patients (aortic regurgitation; $n=48$, aortic stenosis; $n=26$) and 26 healthy subjects, then analyzed them using Janz's method to elucidate local σ in segment #12 (mid-anterolateral) based on AHA/ASE segmentation criteria. Global σ was obtained using Mirsky's formula. A highly significant correlation was found between local σ and global σ ($r=0.99$, $p<0.001$). Bland–Altman analysis also showed good agreement between the two methods (mean bias 2.4 kdyn/cm^2, limits of agreement 9.3 kdyn/cm^2/−4.6 kdyn/cm^2). There were good correlations for both intra-observer and inter-observer agreement. Our novel software package was shown useful to assess local circumferential stress with contemporary cardiovascular imaging techniques.

Myocardial wall stress is an important index of ventricular loading conditions and may be useful to evaluate stress-shortening (EF) or stress-fiber shortening (mVCF) relationships in the LV myocardium [1–3]. Janz proposed a formula for estimating wall stress based on the thick-wall shell theory and a more general representation of ventricular geometry, as opposed to a sphere, cylinder, or ellipsoid [2–5]. This method has been applied for determining local afterload and preload of the myocardium, and can be clinically used for inhomogeneity of wall thickness [4–7]. However, Janz's method requires exact tracing of the margin of the endocardium and epicardium, though it is often difficult to determine the epicardial surface provided by left ventriculography (LVG) in a right anterior oblique (RAO) projection, especially in the basal portion, as well as the thickness of the inferior wall of the ventricle.

Modern advances in high quality three-dimensional imaging techniques for the entire LV have enabled accurate tracing of the margin of the endocardium and epicardium in LV images [6]. We developed a novel software system to provide local circumferential stress that utilizes Janz's method, which is applicable for use with contemporary LV imaging techniques. The aim of the present study was to confirm the validity of our software by comparing local stress values obtained by Janz's method with global equatorial stress values obtained by Mirsky's formula.

LVG records for patients treated for aortic regurgitation ($n=48$) or aortic stenosis ($n=26$) at Osaka University Hospital were analyzed, while those of 26 healthy subjects were also studied. The entire cohort consisted of 76 men and 24 women, ranging in age from 38 to 60 years old (mean age, 45 years).

All 100 subjects underwent cardiac catheterization and left ventriculogram findings were obtained, which allowed for volume and stress analysis. Our catheterization technique has been described previously [7,8]. LVG was performed using biplane 35-mm cineangiography in all of the subjects, with aortic and left-ventricular pressures measured immediately before LVG. The preprocessed data were then directed to another personal computer for computation of various indices of LV function, including volumes, mass, and LVEF.

Our software for assessing local wall stress using Janz's method was applied to the 100 obtained LVG images, each of which were acquired from one cardiac cycle. The images were stored as audio video interleave or bitmap files, and transferred to a computer with the appropriate software installed for offline analysis. Left ventricular endocardial and epicardial borders in the RAO projection were manually traced at end-diastole and end-systole using a workstation. To identify the borders, we determined the sharp outlines between the myocardium and blood pool on the inside, and the myocardium and various structures on the outside. Papillary muscles were cut at their insertions. Correction for movement between end-diastole and end-systole was achieved by positioning at the most apical point.

Local average circumferential stress (local σ) in segment #12 (mid-anterolateral) based on AHA/ASE segmentation criteria [9] was computed using Janz's method [2] as:

$$\text{local } \sigma = P \times AC / AW$$

☆ Presented at the American Heart Association Scientific Sessions, New Orleans, Louisiana, November 8–12, 2008.

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0167-5273/$ see front matter © 2009 Published by Elsevier Ireland Ltd.
doi:10.1016/j.ijcard.2009.05.026

Please cite this article as: Shudo Y, et al, Novel software package for quantifying local circumferential myocardial stress, Int J Cardiol (2009), doi:10.1016/j.ijcard.2009.05.026

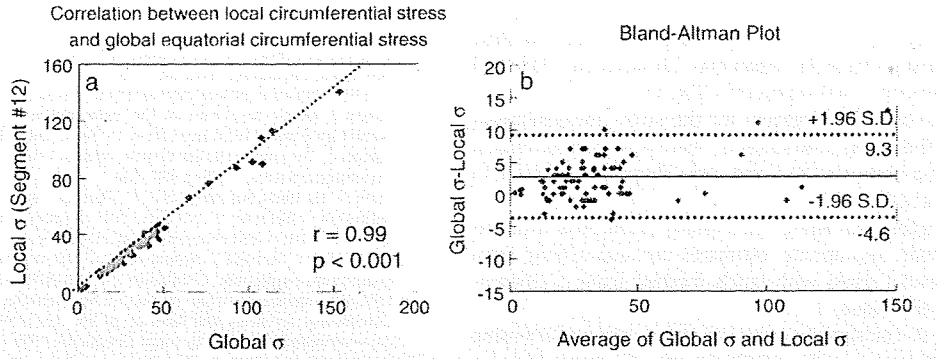

Fig. 1. (a) A highly significant correlation was found between local σ obtained with Janz's method and global σ obtained with Mirsky's formula ($r = 0.99$, $p < 0.001$). (b) Bland–Altman analysis showed good agreement between local σ by Janz's method and global σ by Mirsky's formula (mean bias 2.4 kdyn/cm^2, limits of agreement 9.3 kdyn/cm^2/−4.6 kdyn/cm^2).

where P represents end-diastolic pressure, AC is the cross-sectional area of the LV cavity, and AW is the cross-sectional area of the LV wall at end-diastole in each long-axis plane. Determination of the epicardial surface other than the middle portion of the anterior wall in an RAO projection is sometimes difficult, because of its poor contrast in comparison with the surroundings. In this study, we determined local wall stress only for the mid-anterior portion, which was defined as segment #12 (mid-anterolateral), according to AHA/ASE segmentation criteria [9].

Global equatorial circumferential stress (global σ) was computed using Mirsky's formula [3] as:

$$\text{global } \sigma = 1332 \times (Pb / h_{ed})\left(1 - b^2 / 2a^2 - h_{ed} / 2b + h_{ed}^2 / 8a^2\right)$$

where P represents end-diastolic pressure, h_{ed} represents end-diastolic wall thickness, and a and b are the end-diastolic semi-major and end-diastolic semi-minor axes, respectively, at the midwall.

All measurements and calculations were processed using our newly-developed software while connected to an offline computer. Intra-observer (Y.S.) and inter-observer (Y.S. vs. K.T.) variability for local σ was evaluated using the end-diastolic frames from images obtained from 40 subjects.

Values are expressed as the mean ± 1SD. Linear regression analysis was applied to analyze the relationship between local σ and global σ. Values for local σ obtained with Janz's method [2] and global σ with Mirsky's formula [3] were compared using the method of Bland and Altman [10]. Intra- and inter-observer variability was analyzed using linear regression analysis, and the method of Bland and Altman [10]. We considered results significant at a value of $p < 0.05$.

A highly significant correlation was found between local σ obtained with Janz's method and global σ obtained with Mirsky's

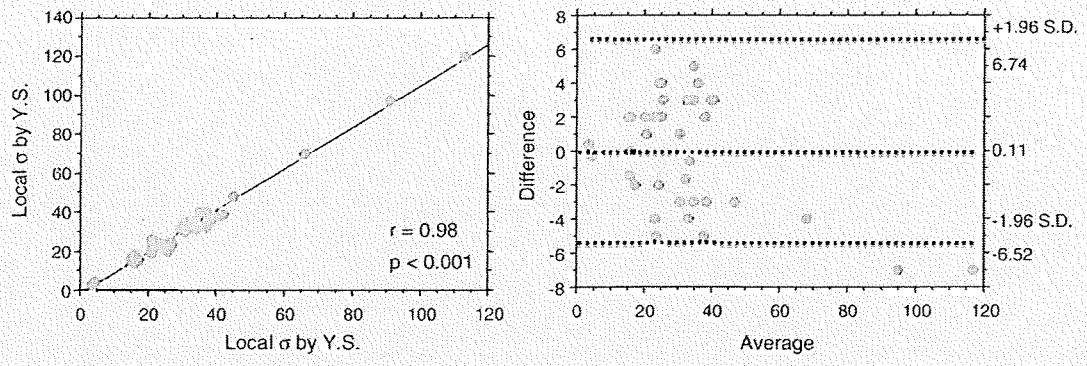

Fig. 2. There was a good correlation for both intra-observer (Y.S.) variability and intra-observer (Y.S.) agreement in stress measurements of 40 subjects.

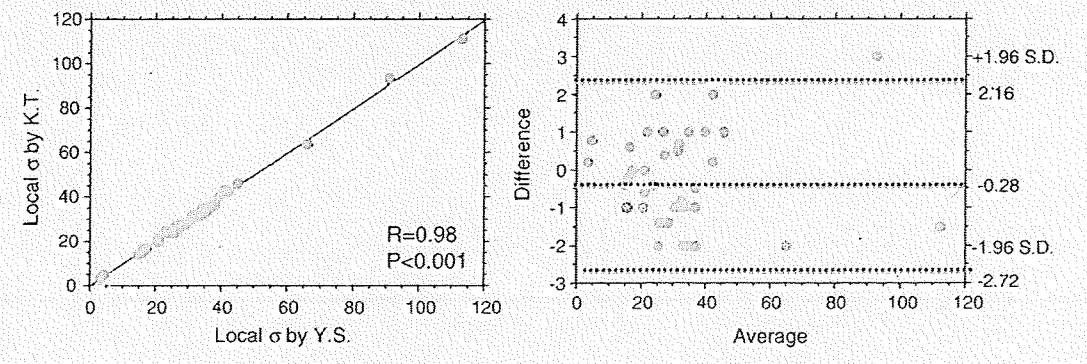

Fig. 3. There was a good correlation for both inter-observer (Y.S. vs K.T.) variability and inter-observer (Y.S. vs. K.T.) agreement in stress measurements of 40 subjects.

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formula ($r=0.99$, $p<0.001$) (Fig. 1). Also, results of Bland–Altman analysis showed good agreement between local σ by Janz's method and global σ by Mirsky's formula (mean bias 2.4 kdyn/cm^2, limits of agreement 9.3 kdyn/cm^2/−4.6 kdyn/cm^2) (Fig. 1).

Intra- and inter-observer agreement for the stress measurements was assessed using the results of 40 subjects. There was good correlation shown for both intra-observer (Y.S.) and inter-observer (Y.S. vs. K.T.) agreement (Figs. 2 and 3).

Our findings suggest that these calculations performed with our software can provide appropriate estimates for quantifying local average circumferential stress with Janz's method using a contemporary LV imaging technique.

Assessments of LV contractility using the stress–strain relationship have been attempted previously [5,7,8], though the most common approach was to use conventional LVG images. Therefore, until recent improvements in advanced imaging tools, estimations of wall stress have met with limited success. In the present study, modern imaging techniques were employed for acquiring image projections and volumetric image reconstruction, which enabled us to estimate wall stress segment by segment with our software. In the future, we intend to assess local circumferential wall stress in patients with wall thickness inhomogeneity, such as that seen in cases of heart disease and ischemic cardiomyopathy.

In conclusion, these results indicate that our novel software package is useful to assess local circumferential myocardial stress using Janz's method with contemporary cardiovascular imaging techniques.

Acknowledgement

The author of this manuscript has certified that he complies with the Principles of Ethical Publishing in the International Journal of Cardiology [11].

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Bcl-2 Expression Enhances Myoblast Sheet Transplantation Therapy for Acute Myocardial Infarction

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Running title: Bcl-2 enhances myoblast sheet transplantation

ABSTRACT

Myoblast sheet transplantation is a promising novel treatment modality for heart failure after an ischemic insult. Low supply of blood and nutrients may, however, compromise sheet survival. The aim of this study was to investigate the effect of mitochondria-protective Bcl-2-modified myoblasts in cell sheet transplantation therapy. In the Bcl-2-expressing rat L6 myoblast sheets (L6-Bcl2), increased expression of myocyte markers and angiogenic mediators was evident as compared to wild type (L6-WT) sheets. The L6-Bcl2 sheets demonstrated significant resistance to apoptotic stimuli, and their differentiation capacity *in vitro* was increased. We evaluated the therapeutic effect of Bcl-2-modified myoblast sheets in a rat model of acute myocardial infarction (AMI). 64 Wistar rats were divided into 4 groups. One group underwent AMI (n=22), another AMI and L6-WT sheet transplantation (n=17), and a third AMI and L6-Bcl2 sheet transplantation (n=20). 5 rats underwent a sham operation. Echocardiography was performed after 3, 10, and 28 days. Samples for histological analysis were collected at the end of the study. After AMI, the Bcl-2-expressing sheets survived longer on the infarcted myocardium, and significantly improved cardiac function. L6-Bcl2 sheet transplantation reduced myocardial fibrosis and increased vascular density in infarct and border areas. Moreover, the number of c-kit positive and proliferating cells in the myocardium was increased in the L6-Bcl2 group. In conclusion,

Bcl-2 prolongs survival of myoblast sheets, increases production of proangiogenic paracrine mediators, and enhances the therapeutic efficacy of cell sheet transplantation.

Key Words: Apoptosis, Bcl-2, Cell Sheet Therapy, Myoblast, Myocardial Infarction

INTRODUCTION

Although the first myoblast transplantation therapies were administered more than a decade ago for the treatment of heart failure (29,34), problems associated with cell injections, such as the massive loss of donor cells, inadequate cell proliferation in the host myocardium, and arrhythmogenicity, remain to be solved. To overcome some of these problems, epicardial transplantation of cell sheets provides a conceptual alternative and a minimally invasive method for cell delivery. In this system, a tissue-engineered multicellular patch or cell sheet is made with a temperature-responsive cell culture dish (22,31). With this technique freely transplantable cell sheets consisting of 3 to 6 million cells can easily be manufactured with no added scaffold material. Such sheets can then be implanted on top of the injured myocardium to which they adhere immediately. Moreover, therapy can be enhanced by piling two or more layers of sheets on top of each other. The superiority of sheet transplantation over intramyocardial injections for cell therapy of heart failure has been demonstrated in both small and large animal studies (12,15,20). The therapeutic effect of cell sheets is considered to be mediated via finite production of paracrine effectors that locally stimulate the underlying injured myocardium. In models of cardiac ischemia and infarction, myoblast sheet therapy has been shown to inhibit fibrosis and to stimulate angiogenesis (20).

These previous studies have shown that multiple myoblast sheets are required for ischemic heart failure therapy. The sheets on the injured myocardium are exposed to apoptotic stress and nutrient deprivation, and thus an increased number of cells are required for therapeutic benefit. In order to reduce the amount of transplanted sheets and to increase their tolerance of the death-promoting host environment, we investigated the effect of *bcl2* gene expression in myoblast sheets and their therapeutic efficacy in a rat model of acute myocardial infarction (AMI).

The family of Bcl-2 proteins comprises several members with anti- or pro-apoptotic functions. Bcl-2 itself is anti-apoptotic, functioning in the mitochondrial pathway by counteracting functions of the pro-apoptotic Bax and Bak, and inhibiting cytochrome c release (26). Bcl-2 overexpression has been shown to promote cell survival and to inhibit cell death induced by such apoptosis-inducers as staurosporine, or by nutrient deprivation (6). Bcl-2 gene therapy has been used in cardiac cell therapy to prevent apoptosis upon cell injection into the myocardium (17,19).

In this study, we evaluated the Bcl-2 expression-mediated effects on L6 myoblast sheets both *in vitro* and *in vivo*. We first compared the apoptosis resistance and gene expression profiles of wild type and Bcl-2-modified L6 myoblast monolayers and sheets. We then expanded these results to an *in vivo* setting, and evaluated the effects of wild type and Bcl-2-overexpressing myoblast sheet transplantation in a rat model of AMI.