

## Department of Cardiovascular Surgery

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### General Summary

The main clinical investigations in our department involved evaluation of alterations in cardiac performance after corrective surgeries. Clinical investigations, including follow-up studies, of valvular and ischemic heart diseases are our main research activities, as are studies of complex congenital anomalies. New treatment approaches utilizing new surgical techniques, new devices, and research outcomes have been attempted and evaluated. We are also conducting several experimental studies with *in vivo* and *in vitro* models. The experimental projects include gene therapy for angiogenesis in ischemic myocardium, a new application of autologous skeletal muscle as an assist device in heart failure, and improvement of cardioplegic solutions used during cardiac arrest. The major activities are described below.

### Research Activities

#### *Basic research*

1. Experimental studies of right ventricular dynamic cardiomyoplasty with autologous skeletal muscle

We have performed an experimental study to test the feasibility of right ventricular (RV) dynamic cardiomyoplasty with a paced skeletal muscle graft wrapped around the RV to augment depressed ventricular function. In 5 beagles, RV dysfunction was produced by ligating the right coronary artery. A pedicled latissimus dorsi muscle graft was transferred to the thorax and wrapped onto the RV free wall as an on-lay patch and electrically stimulated in synchrony with the cardiac beats using a newly developed pacemaker system. Regional function of the RV (percent segmental shortening), assessed with a sonomicrometry real-time functional analysis system, was augmented from 2.6 to 12.1 by pacing the grafts. These results suggest the possible application of the autologous skeletal muscle graft for reconstructive surgery of the RV.

2. A preliminary experimental study of a tissue-engineered dynamic patch utilizing biodegradable polymers

We have performed a preliminary experimental study to establish a tissue-engineering technique for producing a biocompatible dynamic patch utilizing biodegradable polymers seeded with autologous swine cells.

The double-layered scaffold sheets composed of biodegradable polymers (polyglycolic acid mesh) were seeded with different types of cell (myoblasts, skeletal myoblasts

(satellite cells), and bone marrow cells) and compared with non-cell-seeded sheets as a control.

These biodegradable polymers were implanted in the latissimus dorsi muscles of adult pigs for 4 weeks, after which they were explanted to assess histological and biochemical characteristics. The polymers seeded with bone marrow cells and satellite cells became lined with cells immunoreactive to antibodies against alpha-smooth muscle cell antigens, suggesting the angiogenesis of the polymers.

#### *Adult cardiac surgery*

1. Comparison of inflammatory and coronary-graft responses, and quality of anastomoses after off-pump and on-pump coronary bypass surgery

Off-pump coronary artery bypass grafting (OPCAB) has become popular because of potential benefits obtained by elimination of the pump. In this study, we investigated differences in the severity of systemic inflammatory responses by evaluating activation of blood components and the production of proinflammatory substances between OPCAB and conventional coronary artery bypass grafting (cCABG). Changes in eicosanoids and vasoactive substances, the quality of anastomosis, and endothelial smooth-muscle functions of coronary grafts were also assessed and compared. The subjects were 120 patients undergoing OPCAB and 42 patients undergoing cCABG. The mean flow and the pulsatile index were determined for all grafts through measurements of transit time flow. Blood samples were obtained at several points for comparison. The pulsatile index was used to indicate the quality of the anastomosis. The two treatment groups were similar in terms of characteristics, except for evidence of aortic calcification. The average number of grafts did not differ between the groups. However, levels of the creatine phosphokinase MB isozyme were significantly lower in patients undergoing OPCAB. Neither graft flow nor the pulsatile index differed between the groups or among the bypass territories. cCABG was disadvantageous with regard to neutrophil activation (on-pump); however, trends of proinflammatory substances and vasoactive substances (eicosanoids, endothelin) were the same with OPCAB and cCABG. The quality of anastomosis with OPCAB was equivalent to that with cCABG in all territories. OPCAB showed an advantage over cCABG in myocardial protection. Systemic inflammatory responses were somewhat apparent on-pump with cCABG, but the difference disappeared off-pump. Neither coronary-graft responses nor changes in vasoactive substances differed between OPCAB and cCABG.

2. Mitral valve disease: Surgical management of perivalvular leakage after mitral valve replacement

Perivalvular leakage (PVL) is a serious complication after mitral valve replacement. From 1991 through 2006, 9 patients with mitral PVL underwent reoperation. All patients showed severe hemolytic anemia before the operation. The serum level of lactate dehydrogenase decreased from  $2,366 \pm 780$  to  $599 \pm 426$  IU/L after operation. The locations of PVL could be accurately determined with echocardiography in 7 patients. PVL occurred around the posterior annulus in 3 patients, the anterior annulus in 2 patients, the anterolateral commissure in 1 patient, and the posteromedial commissure in 1 patient. The most frequent cause of PVL was annular calcification, which

occurred in 5 patients. Postoperative infection developed in only 1 case. The prosthesis was replaced in 4 patients, and the leak was repaired in 5 patients. There was 1 operative death due to multiple-organ failure and 4 late deaths, due to cerebral infarction, subarachnoid hemorrhage, sudden death, and congestive heart failure due to persistent PVL in 1 patient each. Reoperation for PVL due to extensive annular calcification is associated with a high mortality rate and a high recurrence rate, making such procedures a frustrating challenge for surgeons.

3. Aortic valve disease: Patient-prosthesis mismatch may be irrelevant after aortic valve replacement with the 19-mm Perimount pericardial bioprosthesis in patients 65 years or older

We evaluated valve function and the effects of patient-prosthesis mismatch (PPM) on the medium-term results after implantation of a 19-mm Carpentier-Edwards Perimount (CEP) pericardial aortic valve in patients 65 years or older. From August 1996 through May 2005, 51 patients underwent aortic valve replacement with a 19-mm CEP valve. The mean follow-up period was  $2.4 \pm 1.8$  years, with a total follow-up of 134.4 patient-years. The mean age and body surface area at the time operation were  $74.0 \pm 5.0$  years and  $1.41 \pm 0.14$  m<sup>2</sup>, respectively. There were 2 (3.9%) operative deaths. Three patients (5.9%) underwent enlargement of a small aortic annulus. The actuarial survival rate after 8 years (including operative mortality) was  $90.2 \pm 4.7\%$ . The mean rates of freedom from thromboembolism, from reoperation, and from valve-related mortality at 8 years were  $75.0 \pm 21.7\%$ ,  $97.8 \pm 2.2\%$ , and  $95.3 \pm 3.2\%$ , respectively. The peak and mean transvalvular pressure gradients were significantly improved after surgery (peak:  $93 \pm 35$  vs.  $28 \pm 12$  mmHg; mean:  $58 \pm 19$  vs.  $17 \pm 7$  mmHg;  $p < 0.01$ ). The mean left ventricular mass index had decreased from  $192 \pm 44$  to  $142 \pm 46$  g/m<sup>2</sup> at late follow-up ( $p < 0.01$ ). The prevalence of PPM was low (17.6%) when an indexed effective orifice area of less than 0.85 cm<sup>2</sup>/m<sup>2</sup> was used to indicate significant PPM. The clinical outcome, postoperative pressure gradient, and reduction of left ventricular mass index did not differ between patients with and without PPM. Use of the 19-mm CEP valve achieved satisfactory medium-term clinical outcomes (regardless of PPM) in patients 65 years or older, who are presumed to be less active than are younger patients. Moderate PPM was rare and did not have an adverse effect on the medium-term results. Annulus enlargement was needed only in a few patients when a 19-mm CEP valve could not be inserted.

4. A 10-year study of the durability of triangular resection for prolapsing mitral anterior leaflets

The reconstruction technique of using artificial chordae for prolapsing anterior leaflets has been widely adopted. Since 1991, we performed triangular resection with or without wrapping and shortening of elongated chordae whenever possible instead of using artificial chordae. The aim of this study was to assess long-term results of mitral valve repair, with a focus on the resection of anterior leaflets. From October 1991 through December 2006, we performed mitral valve repair for 57 patients (22 patients have been followed up for more than 10 years) with prolapsing anterior leaflets. Thirty-nine patients underwent triangular resection (14 patients have been followed up for more than 10 years), 16 patients underwent wrapping and shortening of elongated

chordae (13 patients have been followed up for more than 10 years), 9 patients underwent artificial chordal replacement (2 patients have been followed up for more than 10 years), and 4 patients were treated with the flip-over method. Both the anterior and posterior leaflets were resected in 18 patients (8 patients have been followed up for more than 10 years), including 9 patients who underwent wrapping and shortening of elongated chordae. Ring annuloplasty was performed in all patients. A Carpentier-Edwards rigid ring was used in 49 patients. A Physio and Cosgrove ring or band was used in 6 and 2 patients, respectively (average ring size, 30 mm). The mean follow-up duration was 6.2 years (range, 0.5-14 years). The mean age was  $51.7 \pm 15.9$  years. The mean postoperative mitral valve area did not differ significantly among the 3 groups (anterior leaflet resection:  $2.86 \text{ cm}^2$ ; posterior leaflet resection:  $2.86 \text{ cm}^2$ ; anterior and posterior leaflet resection:  $3.09 \text{ cm}^2$ ). Reoperation was required in 4 cases. Two cases were observed within 2 years after we began to perform mitral reconstruction (when we did not perform intraoperative transesophageal echocardiography). One of the reoperated cases, reconstructed with artificial chordae, showed mitral tethering with progression of cardiomyopathy. The other case showed Barlow's disease and was treated with artificial chordae replacement. Fifty-three patients (92%) were in New York Heart Association class I. The linearized rate of thromboembolism did not differ significantly between patients who underwent triangular resection of anterior leaflets (0.57% patient-year) patients who underwent quadrangular resection of the posterior leaflets (0.27% patient-year). There were 2 late deaths: 1 was due to pneumonia and 1 was due to sudden death. The rates of survival and of freedom from reoperation at 10 years were 91.7% and 92.3%, respectively, in patients who underwent resection of the anterior leaflet and both the anterior and posterior leaflets and were 96.4% and 90.4%, respectively, in patients who underwent quadrangular resection of the posterior leaflets; the rates did not differ significant difference between the treatment groups. Moreover, the rates of survival and freedom from reoperation in patients who underwent triangular resection of anterior prolapsing leaflets and were followed up for more than 10 years were 95.2% and 90.0%, respectively. There was no significant difference in the rate of survival or the risk of reoperation between patients who underwent resection of only the anterior leaflet and patients who underwent resection of both the anterior and posterior leaflets. In conclusion, with follow-up extending beyond 10 years, there was no significant difference in the rates of reoperation and survival after resection of the anterior leaflet, the posterior leaflet, and both leaflets. The mitral valve area was in the lower-normal range after anterior leaflet resection, and the remaining mitral valve area was large enough to allow valvular function. Long-term follow-up shows that triangular resection of the prolapsing anterior leaflet is a reliable procedure in terms of obtaining an ideal, smooth coaptation zone.

#### *Surgery for congenital cardiac defects*

1. Studies of myocardial protection during open-heart surgery

1) Experimental studies of a new strategy for myocardial protection against ischemia/reperfusion injury:

On the basis of the results of a series of experimental studies of cardiac ischemia/

reperfusion injury in an in-vivo pig model, we established the efficiency and reliability of intraoperative myocardial protection with integrated myocardial protection using a modification of the combined use of modified St. Thomas solution. Furthermore a recent experimental study of a hybrid cardioplegia solution (blood and crystalloid) demonstrated the critical importance of lowering  $\text{Ca}^{2+}$  content during blood cardioplegic reperfusion (terminal hot shot). More recently, we have performed experimental studies to examine the effects on reperfusion injury of a phosphodiesterase (PDE) III inhibitor added to the cardioplegic solution.

## 2) A high-dose PDE inhibitor in terminal warm-blood cardioplegia

To test the hypothesis that myocardial ischemia/reperfusion injury can be limited by adding a PDE inhibitor to the terminal warm-blood cardioplegia (TWBCP) solution, 25 piglets were placed on cardiopulmonary bypass (CPB) and subjected to 90 minutes of ischemia with a single dose of cold crystalloid cardioplegia solution and reperfusion with or without TWBCP before aortic declamping. Left ventricular functional recovery, assessed with left-ventricular-pulmonary-vein loops with sonomicrometry, and biochemical myocardial injury, evaluated with troponin-T, creatine kinase, and lipid peroxide, were compared among control piglets that did not receive a TWBCP solution, piglets receiving a low-Ca TWBCP solution, and piglets receiving a low-Ca TWBCP solution with amrinone or orprinin.

A significant improvement in cardiac function and a reduction in reperfusion-induced biochemical injury, associated with an increase in myocardial cAMP levels and suppression of lipid peroxide levels, were observed in piglets receiving a low-Ca TWBCP solution with amrinone or orprinin. On the basis of these results, we conclude that a high dose of a PDE III inhibitor in the TWBCP solution replenishes the myocardial cAMP that is depleted during ischemia/reperfusion and promotes rapid and sustained myocardial functional recovery due to the inhibition of oxidative damage.

We are now conducting a dose-response study with the PDE inhibitor orprinin for a future clinical trial of this new therapeutic modality.

## 3) Efficiency of ischemic postconditioning

We have performed experimental studies of ischemic postconditioning in an in vivo pig model of ischemia/reperfusion on CPB. Postconditioning of the ischemic myocardium was applied in 6 pigs, by 10 cycles of transient (10 seconds) ischemia/reperfusion before aortic declamping following 90 minutes of ischemia (aortic clamping) on CPB. Reversal of reperfusion injury, assessed on the basis of left ventricular functional recovery and biochemical injury (l-p-o-, creatine phosphokinase, and troponin), was noted only marginally in 6 piglets. Further studies using an alternate postconditioning strategy with TWBCP are in progress.

## 2. Clinical studies of management of CPB in infants

1) Deleterious effects of hyperoxemia and the role of normoxemic management of CPB  
Because CPB simultaneously alters many factors, including cytokine, vasoactive mediators, and free radical generation, oxidative injury may occur owing to conventional hyperoxic CPB in the heart and lungs of infants. To test the hypothesis that the extremely high  $\text{pO}_2$  level during CPB provokes oxidative cardiopulmonary changes that can be prevented by normoxemic CPB management, we performed a clinical study to

compare functional and biochemical effects after CPB in infants who underwent normoxemic management ( $pO_2$ , 100 to 150 mmHg) or hyperoxemic management ( $pO_2$ , 200 to 300 mmHg). Respiratory and myocardial function and results of routine enzymatic evaluation did not differ significantly between the treatment groups. However, normoxemic management was more beneficial for cytokine generation and pulmonary vasoconstriction after CPB in infants with pulmonary hypertension. The present study suggests cardiopulmonary bypass causes a substantial inflammation stress, including oxidative lipid peroxidation, and that these deleterious effects are prevented by normoxemic CPB management

## 2) Effects of modified ultrafiltration after operation for congenital heart disease with pulmonary hypertension

The systemic inflammatory response after CPB is a key factor in the incidence of postoperative pulmonary hypertensive crises in children. To evaluate the effect of modified ultrafiltration (MUF) on the ability to remove chemical mediators, hemodynamics, and pulmonary function, we studied infants with a ventricular septal defect and pulmonary hypertension who underwent a venovenous MUF after CPB. Chemical mediators (levels of thromboxane  $B_2$ , interleukin 6, and endothelin 1), pulmonary function ( $PaO_2/FiO_2$ , A-a $DO_2$ , and the respiratory index), and the reduction in the ratio of pulmonary arterial pressure to aortic pressure were evaluated before and after MUF.

The use of MUF produced significant improvements in respiratory function and pulmonary artery pressure, associated with marked reductions in the levels of thromboxane  $B_2$ , interleukin 6, and endothelin 1. In addition, the use of MUF significantly decreased the incidence of postoperative pulmonary hypertensive crises compared with that in a historical control group without MUF. On the basis of these findings, we conclude that MUF is useful for avoiding pulmonary disorders due to CPB, especially in pediatric patients with preoperative pulmonary hypertension.

## 3. Clinical studies on pediatric heart surgery

### 1. Retrospective study of the indications and outcomes of the Fontan procedure

The clinical studies were undertaken by reviewing clinical records and data of patients who underwent staged univentricular repair, including the bidirectional Glenn procedure and the Fontan procedure, and examined: 1) the efficacy of the staged approach for high-risk Fontan candidates and selection criteria; 2) risk analysis with a newly proposed index: the Fontan index; 3) indications for final Fontan conversion after the staged approach assessed on the basis of superior vena cava pressure at Glenn circulation; 4) the clinical importance and limitations of the early volume reduction strategy as a infantile surgical policy for Fontan candidates; and 5) persistent hypoxia after the bidirectional Glenn procedure, and therapeutic management.

### 2. New approach for intraoperative evaluation of hemodynamic candidacy for the Fontan procedure after the bidirectional Glenn procedure

In 6 patients in whom the staged Fontan procedure was indicated after the bidirectional Glenn procedure, we measured superior vena cava flow, which is equivalent to pulmonary artery flow in bidirectional Glenn procedure physiology, by means of a transit-flow meter intraoperatively. Measurement of pulmonary flow and pulmonary vascular

resistance, incorporated with serial volume loading, allows the pulmonary vascular reserve capacity to be assessed in response to an increase in pulmonary flow to simulate Fontan circulation. In 4 patients in whom pulmonary artery flow increased to 2.0 L/min/body surface area under the acceptable range of central venous pressures (i.e., less than 15 mmHg), Fontan completion was successfully performed with excellent hemodynamic status.

### 3. Ross procedure

The surgical outcome and long-term results of the Ross procedure were reviewed, with a focus on autograft durability, in 33 patients who underwent the Ross procedure from 1995 through 2007 with total aortic root replacement and use of a pulmonary autograft. Autograft function was assessed with periodic echocardiographic evaluation for up to 12 years after the operation. There were no operative or acute deaths, but late reoperation for autograft regurgitation was necessary in 3 patients: (rate of freedom from reoperation for autograft failure, 87% at 12 years). The durability of implanted pulmonary autograft valves was excellent, especially in pediatric patients and patients with preoperative aortic stenosis.

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