Department of Cardiovascular Surgery

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General Summary

The main investigations in our department involved clinical study, evaluation of changes in cardiac performance, and long-term outcomes of corrective surgery, and experiments to address clinical problems we are facing. Clinical investigations, including follow-up studies, of valvular and ischemic heart diseases, are a focus of our clinical research activities, as are studies of complex congenital anomalies. New treatment approaches taking advantage of new surgical techniques, devices, and research outcomes have been investigated and attempted. We are also performing several experimental studies with *in vivo* and *in vitro* models. The experimental projects include the application of autologous skeletal muscle as an assist device in heart failure, protection of the lung during extracorporeal circulation, and improvement of cardioplegic solutions during cardiac arrest. The major activities are described below.

Research Activities

Basic research

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 integrated intraoperative myocardial protection with modified St. Thomas' solution. Furthermore, a recent experimental study of hybrid cardioplegia (blood and crystalloid cardioplegia) demonstrated the critical importance of lowering Ca^{2+} content during blood cardioplegic reperfusion (terminal hot shot). More recently, we have performed experimental studies to examine the effect on reperfusion injury of a phosphodiesterase (PDE) III inhibitor added to the cardioplegic solution.

2) A high dose of PDE III inhibitor in terminal warm blood cardioplegia

To test the hypothesis that myocardial ischemia/reperfusion injury can be limited by adding a PDE III inhibitor to terminal warm blood cardioplegia (TWBCP), 25 infant piglets were placed on cardiopulmonary bypass (CPB) and subjected to 90 minutes of ischemia with a single dose of cold crystaroid cardioplegia, and reperfusion with or without TWBCP before aortic declamping. Left ventricular (LV) functional recovery assessed with LV pressure-volume loops with sonomicrometry and biochemical myocar-

dial injury evaluated wtih levels of troponin-T, creatine kinase (CK), and lipid peroxide were compared among group I (control without TWBCP), group II (low-Ca TWBCP), and group III (low-Ca TWBCP with the PDE inhibitor olprinone).
A significant improvement in cardiac function and a reduction in reperfusion-induced biochemical injury, associated with a marked suppression of the lipid peroxide level, were noted in Group III. On the basis of these results, we conclude that a high dose of a PDE III inhibitor in the TWBCP promotes rapid and sustained myocardial functional recovery and inhibits oxidative biochemical damage.

3) Efficiency of ischemic postconditioning: Reversal of myocardial injury after cardioplegic arrest with ischemic postconditioning during early reperfusion

This study tested the hypothesis that the myocardial damage induced by ischemia/reperfusion can be reduced by ischemic postconditioning early during reperfusion.
Methods: Eighteen piglets weighing 10.3±1.5 kg subjected to 90 minutes of ischemia with single-dose crystalloid cardioplegia followed by 60 minutes of reperfusion on CPB. In 12 of the piglets, the 2 types of ischemic postconditioning strategies — 6 cycles of 10 seconds of ischemia/reperfusion (protocol I) or 3 cycles of 30 seconds of ischemia/reperfusion (protocol II) — were applied before aortic unclamping, whereas the other 6 piglets were not treated (Control). The LV function (systolic/diastolic) was evaluated with end-systolic elastance (Ees) and the LV diastolic time constant during isovolumic relaxation (tau). Myocardial and blood levels of lipid peroxide, troponin T, and CK were measured.
Results: In the control group both systolic and diastolic LV dysfunction (depressed Ees: 54±14% of preischemic value and increased tau (240%±38%) associated with oxidant-induced biochemical injury (increased CK, troponin, and lipid peroxidates) were noted after 90 minutes of cardioplegic ischemia followed by untreated reperfusion. In contrast, postconditioning, especially with protocol II, allowed significantly better LV functional recovery (%Ees: protocol I, 67%±23%; protocol II, 130±43%*; *$p<0.01$ vs. control group, 54%±14%), tau (%tau: protocol I, 140%±60%*; protocol II, 123%±43%*; *$p<0.01$ vs. control group, 240%±38%), and less myocardial biochemical injury (myocardial lipid peroxide: 123±21*; and 134%±12%*; *$p<0.05$ vs. 180±34). Also, serum levels of CK, troponin, and lipid peroxide were reduced in both postconditioning groups.
Conclusion: Ischemic postconditioning during early reperfusion produces prompt myocardial functional recovery with decreased biochemical injury in an *in-vivo* piglet CPB model. The interval and duration of repeated brief ischemia/reperfusion during postconditioning might be crucial to determine the beneficial effects of ishemic postconditioning.

2. Clinical studies of the management of CPB in infants

1) Deleterious effect of hyperoxemia and the role of continuous infusion of human atrial natriuretic peptide

Because CPB simultaneously alters many factors, including cytokines, vasoactive mediators, and free radical generation, oxidative injury due to conventional hyperoxic CPB might occur in the infantile heart and lung. To test the hypothesis that the extremely high pO_2 levels during CPB induce oxidative cardiopulmonary changes, which can be

modulated by continuous infusion of human atrial natriuretic peptide (hANP), we performed a clinical study to compare functional and biochemical effects after CPB in infants. There was no significant difference in respiratory or myocardial function or results of routine enzymatic evaluation between infants who were or were not treated with continuous infusion of hANP. However, continuous infusion of hANP had beneficial effects on cytokine generation and pulmonary vasoconstriction after CPB in infants with pulmonary hypertension. The present study suggests cardiopulmonary bypass causes a substantial inflammatory stress including oxidative lipid peroxidation and that these deleterious effects are at least partially prevented by continuous infusion of hANP

Congenital cardiac surgery

Clinical studies of pediatric heart surgeries

1. Fontan operation

Clinical studies reviewed the clinical records and data of patients who underwent staged univentricular repair, including the bidirectional Glenn procedure (BDG) and Fontan-type operations, and 1) demonstrated the efficacy of the staged approach for high-risk candidates for the Fontan procedures and its indications; 2) examined risk analysis with a newly proposed index: the Fontan index; 3) assessed indications for the final Fontan conversion after the staged approach assessed by superior vena cava pressure during Glenn circulation; 4) clinical importance and limitation of the early volume-reduction strategy as an infantile surgical policy for Fontan candidates; 5) examined persistent hypoxia after BDG, and therapeutic management; and 6) involved the intraoperative evaluation of hemodynamic candidacy for the Fontan operation after BDG.

In 9 patients, in whom the staged Fontan procedure was indicated after BDG, we measured superior vena cava flow, which is equivalent to pulmonary artery flow in BDG physiology, by means of a transit-flow meter intraoperatively. Measurement of pulmonary artery flow and pulmonary vascular resistance, incorporated with serial volume loading, allowed the assessment of the pulmonary vascular reserve capacity in response to an increase in pulmonary flow to simulate Fontan circulation. In 4 patients in whom pulmonary artery flow had increased to as high as 2.0 l/min/body surface area under the acceptable range of central venous pressure (i.e., <15 mmHg), Fontan completion was successfully performed with excellent hemodynamic status.

2. Ross operation

The surgical outcome and long-term results of the Ross operation were reviewed, with a focus upon autograft durability, in 33 patients who underwent the Ross procedure from 1995 through 2007 with total aortic root replacement and pulmonary autografting. Autograft function was assessed with periodical echocardiographic evaluation postoperatively for as long as 12 years. There were no operative or acute deaths, but late reoperation was required for autograft regurgitation in 3 patients: (rate of freedom from reoperation for autograft failure: 87% over 12 years). Excellent durability of implanted pulmonary autograft valves was noted, especially in pediatric patients and in patients with preoperative aortic stenosis.

Adult cardiac surgery

Clinical studies

1) Patient-Prosthesis Mismatch: The Jikei Experience

Patient-prosthesis mismatch (PPM) was defined as being present "when the effective prosthetic valve area, after insertion into the patient, is less than that of a normal valve." However, on the basis of the correlation between the mean transvalvular pressure gradient and the corrected effective orifice area, PPM is currently defined as an effective orifice area divided by body surface area of $\leq 0.85\ cm^2/m^2$. The surgical procedure will differ for each patient because of variations in the size of the aortic annulus and because of the patient's age, sex, level of activity, level of motivation, and complications. However, the risk of PPM should always be minimized through the selection of appropriate surgical strategies, including aortic root enlargement, use of a supra-annular or high-performance prosthesis, and the use of a stentless bioprosthesis, aortic homograft, or pulmonary autograft. We reviewed our results for aortic valve replacement, when we routinely performed aortic root enlargement in patients younger than 65 years, while supra-annular implantation of a bioprosthesis (Carpentier-Edwards Perimount valve) was performed for patients 65 years or older with a small aortic annulus. Annular enlargement in active young adults may be contributing to longer survival and better quality of life. The smallest bioprosthetic valve (19 mm in diameter) rarely led to PPM in older patients, and the presence of PPM did not have negative effects on late survival.

2) Present and future aortic valve selection based on current guidelines

The choice of a mechanical or tissue valve to replace the aortic valve remains controversial. According to the guidelines of the American College of Cardiology/American Heart Association and the Japanese Circulation Society, based on recent reports of excellent long-term performance of bioprosthetic valves, we have chosen tissue valves as the most appropriate aortic valve for elderly patients. In patients younger than 65 years, tissue valves are becoming popular regardless of the second operation. The purpose of this study was to examine the appropriateness of our valve selection and to compare 12-year results after aortic valve replacement with mechanical and bioprosthetic valves in recent years. There was no difference in survival between the 2 groups. Few patients younger than 65 years would select a bioprosthetic valve after being informed of the advantage of an anticoagulation-free life. The main reasons for not using a bioprosthetic valve were the possibility of swine vesicular disease and the risk of reoperation. The clinical decision about the choice of aortic valve, based on the current guideline, would be appropriate and reasonable.

3) Mitral valve reconstruction: leaflet resection and suturing techniques

Mitral valve repair for mitral insufficiency is widely favored over valve replacement. We have enthusiastically performed resection and suturing of the prolapsed anterior and the posterior leaflets. We evaluated these results. The rates of freedom from reoperation at 10 years were 93%±5% for triangular resection in the anterior leaflet and 96%±3% for quadrangular resection in the posterior leaflet and did not differ significantly. Recently, we have performed triangular resection rather than quadrangular even for posterior and commissural lesions. This change completely eliminated late dehiscence

and leakage at the resected area by reducing annular stress.

4) Mitral valve ring

Prosthetic annuloplasty rings play an important role in mitral valve repair. This study was performed to evaluate the midterm results of the Carpentier-Edwards rigid ring, the Physio ring, and the Cosgrove band. From October 1991 through December 2005, 140 patients underwent mitral valve repair with the rigid ring (121 patients), the Physio ring (9 patients), or the Cosgrove band (10 patients). The mitral valve disease was degenerative in all patients. The Cosgrove band was used exclusively for posterior lesions. All patients were followed up with echocardiography. Sizes of rigid ring we have used ranged from 26 to 36 mm, with 30 mm being most common. Although the mitral orifice area was decreased after mitral valve repair in all patients, particularly in patients treated with the classic ring, no patients required reoperation because of mitral stenosis or left outflow obstruction (systolic anterior motion). Postoperative volume reductions of the LV at systole and diastole were observed. Ejection fractions were unchanged in all cases. The actuarial survival rate was 92.0%±3.0% at 10 years. The rate of freedom from reoperation at 10 years was 96.0%±2.0%. By remodeling the enlarged annulus, the rigid ring has yielded promising midterm results in terms of the rates of survival and freedom from reoperation. However, use of a band may be reasonable if annular movement is desired.

5) Evaluation of a new portable device for measuring prothrombin time—international normalized ratio after cardiac surgery

We evaluated a new portable device (CoaguChek XP, Roche Diagnostics) for measuring the prothrombin time—international normalized ratio (PT-INR) in 63 patients after cardiac surgery and compared the results with those of the conventional method. There was a strong correlation between the PT-INR values measured conventionally and those obtained with the CoaguChek XP. This new device was easy to use, data were obtained rapidly, and the results were reliable. The CoaguChek XP will be particularly useful for outpatients. PT-INR self-management is expected to be introduced as soon as health insurance coverage is obtained.

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