Department of Cardiovascular Surgery

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General Summary

The main activities in our department involved clinical study, evaluation of alterations in cardiac performance and long-term results after corrective surgeries, and experimental study 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. The recently increased incidence of aortic aneurysm has become another concern in our field. New treatment approaches applying new surgical techniques, new devices, and research outcomes have been investigated and attempted. We also are performing several experimental studies with in vivo models. The experimental projects involve protection of the lung during extracorporeal circulation and postischemic conditioning after cardiac arrest. The major activities are described below.

Research Activities

Basic research

I Studies of myocardial protection during open-heart surgery

1. Experimental study of a new strategy for myocardial protection against ischemia/reperfusion injury

1) Preventing reperfusion injury and ensuring prompt functional recovery after prolonged global ischemia in piglet hearts with a high-dose phosphodiesterase III inhibitor at controlled reperfusion with blood cardioplegic arrest

In addition to having inotropic and vasodilatory effects, phosphodiesterase (PDE) III inhibitors protect against ischemia and reperfusion. However, these drugs, particularly during the early reperfusion phase, have yet to be assessed in clinically relevant in vivo models. We examined the effects of high-dose olprinone, a PDE III inhibitor, with terminal warm-blood cardioplegia (TWBCP) with respect to reversing myocardial reperfusion injury.

Fifteen piglets were placed on cardiopulmonary bypass (CPB) and subjected to 90 minutes of global ischemia, followed by 30 minutes of reperfusion. The animals were divided in 3 groups. In group I, the control group, TWBCP was not supplemented; in group II, TWBCP was supplemented; and in group III, TWBCP was supplemented with olprinone. Myocardial performance was evaluated before and after CPB, after which total electrical cardioversion after reperfusion was measured. Levels of troponin-T and

lipid peroxide were measured. Concentrations of olprinone in TWBCP, serum, and myocardial tissue were measured.
Group III with olprinone showed significant performance recovery (81.9±24.5%; $p<0.01$ vs. groups I and II) without electrical cardioversion. Levels of troponin-T and lipid peroxide in group III were lower than those in group I or II ($p<0.01$ vs. group I; $p<0.05$ vs. group II). Olprinone concentrations in group III were within the range of 200 ng/ml doses having negligible inotropic and dilatory effects. We conclude that TWBCP supplemented with high-dose olprinone reduces myocardial ischemia/reperfusion injury by reducing oxidant-mediated lipid peroxidation and that olprinone has myocardial protective effects.
2) Effect of postconditioning: Experimental study using an in vivo piglet model for cardiovascular surgical on reversal of myocardial stunning by ischemic postconditioning
This study tested the hypothesis that ischemia/reperfusion—induced myocardial damage can be reduced by ischemic postconditioning during the early phase of reperfusion. Eighteen piglets with a mean weight of 10.3±1.5 kg underwent 90 minutes of ischemia with single-dose crystalloid cardioplegia followed by 60 minutes of reperfusion on CPB. In 12 of the piglets, the 2 ischemic postconditioning strategies—6 cycles of 10 seconds of ischemia/reperfusion (PC-I) or 3 cycles of 30 seconds of ischemia/reperfusion (PC-II)—were applied before aortic unclamping, whereas the other 6 piglets were not treated (control). Left ventricular (LV) function (systolic/diastolic) was evaluated with end-systolic elastance (Ees) and the LV time constant for pressure decay during isovolumic relaxation (Tau). Myocardial and blood levels of lipid peroxide, troponin-T, and creatine kinase were measured.
Both systolic and diastolic LV dysfunction (depressed Ees: 54±14% of preischemic value, and increased Tau: 240%±38%), associated with oxidants induced biochemical injury (increased creatine kinase, T-troponin, and lipid peroxidates), were noted after 90 minutes of cardioplegic ischemia followed by untreated reperfusion in the control group. In contrast, postconditioning, especially with protocol II, allowed significantly better LV functional recovery (% Ees: PC-I, 67%±23%; protocol II, 130±43%*; *$p<0.01$ vs. control group, 54%±14%. % Tau: PC-I, 140%±60%*; PC-II, 123%±43%*; $p<0.01$ vs. control group, 240%±38%), and less myocardial biochemical injury (myocardial lipid peroxide: PC-I, 123±21%*; PC-II, 134±12%*; $p<0.05$ vs. control group, 180±34%). Also serum levels of creatine kinase, troponin, and lipid peroxide were decreased in the both postconditioning groups.
Ischemic postconditioning during the early phase of reperfusion produced 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 ischemic postconditioning.

Pediatric heart surgery

1. Fontan operation

1) Long-term results of the lateral tunnel Fontan procedure with autologous tissue
A review of clinical records and data of patients who had undergone staged

univentricular repair, including the bidirectional Glenn (BDG) procedure and the Fontan procedure, demonstrated excellent long-term results (10-year postoperative survival rate=96.7%) after a lateral tunnel Fontan procedure with autologous tissue.

2) Coagulability and fibrinolytic function in Fontan circulation: Possibility of the conversion of anticoagulation therapy

There is still no consensus regarding the postoperative use and duration of warfarin adminstration after the Fontan procedure. Recently, we have evaluated changes in coagulability and fibrinolytic function after surgery and then modified the anticoagulation therapy for patients to normalize coagulability and fibrinolytic function. We have measured plasma levels of thrombin antithrombin-3 complex (TAT) as the index of coagulability and α2-plasmin inhibitor-plasmin complex (PIC) as the index of fibrinolytic function in 20 patients who had undergone the extracardiac Fontan procedure (mean age at operation, 4.2 years) without complications. In all patients, intracardiac thrombus was also detected with primarily transthoracic echocardiography during the period of this study. The mean follow-up duration was 18.7 months (range, 6 to 60 months). No late deaths or thromboembolism occurred in these patients. Levels of both TAT and PIC remained higher than normal for 6 months after surgery, even in patients receiving warfarin. The values then began to gradually decline and had almost completely normalized by 12 months. Confirming these results, we have changed anticoagulation therapy from warfarin to antiplatelet agents for such cases. After this change, plasma levels of TAT and PIC have remained lower, and no patient showed thromboembolic event in echocardiography.

This study suggests that Fontan patients might need warfarin for anticoagulation therapy for the first year after surgery, because of their activated status of coagulability. However, warfarin could be replaced by an antiplatelet agent for patients who show normal results, and no major complications have occurred for 12 months after surgery. We are also reminded that further evaluation and follow-up are important and necessary.

3) Intraoperative evaluation of pulmonary flow reserve capacity and a new method for predicting post-Fontan hemodynamic status

In 12 patients for 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-flowmeter intraoperatively. Measurement of pulmonary artery flow and peripheral vascular resistance, incorporated with serial volume loading, allow the assessment of pulmonary vascular reserve capacity in response to an increase in pulmonary flow to simulate Fontan circulation. The pulmonary vascular reserve capacity, assessed with the percent reduction in pulmonary resistance in response to increased pulmonary flow, was revealed to be a strong indicator for post-Fontan outcome and the final central venous pressure (CVP) at Fontan circulation. In 8 patients who underwent the Fontan operation, there was a significant relationship between the actual CVP and the CVP predicted by means of intraoperative simulation.

2. Surgical outcomes and long-term results of the Ross operation: Effect of autograft dilatation

Surgical outcomes and long-term results were reviewed, with a focus on autograft durability, in 35 patients who had undergone the Ross procedure from 1995 through

2008 with total aortic root replacement and pulmonary autografting. Autograft function was assessed with periodic echocardiographic evaluations for up to 14 years after the operation. There was no operative or acute deaths or late reoperations for autograft regurgitation in 3 patients: (% freedom from reoperation for autograft failure, 87% over 14 years). Excellent durability of the implanted pulmonary autograft valve was noted, especially in children and in patients with preoperative aortic stenosis.

Adult cardiac surgery

1. Ten-year results of aortic valve replacement with the Carpentier-Edwards pericardial bioprosthesis: Consideration of patient-prosthesis mismatch

From June 1996 through March 2008, 244 patients underwent aortic valve replacement with a Carpentier-Edwards pericardial valve. Their mean age was 69.8±6.4 years. The patients received a 19-mm valve (n=53), a 21-mm valve (n=87), a 23-mm valve (n=80), or a 25-mm valve (n=24). The survival rate was 91.8% at 5 years and 87.2% at 10 years. The rate of freedom from valve-related death was 98.2% at 10 years. The patients with patient-prosthesis mismatch, as indicated by an indexed effective orifice area (IEOA) less than 0.85 cm^2/m^2, did not have poorer outcomes. Moreover, the mean pressure gradient on postoperative echocardiography in these patients was greater than 10 mmHg. We conclude that the hazard point of an IEOA of 0.85 cm^2/m^2 for patient-prosthesis mismatch should be reconsidered.

2. Electron beam cine computed tomography—based evaluation of left atrial function after the maze procedure for mitral valve regurgitation

There has been little study of whether atrial function is equally restored by surgery in patients with mitral regurgitation and atrial fibrillation and in patients with mitral regurgitation and sinus rhythm.

We measured atrial volume with electron beam tomography, which has excellent temporal resolution and minimizes motion artifacts, and used the data to construct left atrial volume-time curves. The subjects were 33 patients with or without atrial fibrillation who had undergone surgery for mitral regurgitation and 11 control patients.

In patients with sinus rhythm, left atrial volume decreased significantly, regurgitation resolved soon after surgery, and the reserve function was well maintained. Left atrial booster pump function was also well maintained before and after surgery. In patients with atrial fibrillation that resolved after maze surgery, the left atrial volume was larger immediately after surgery than that in patients who had sinus rhythm and did not improve in the postoperative period. These patients had lower reserve function and much lower booster pump function despite restoration of sinus rhythm. Patients with mitral regurgitation and atrial fibrillation that spontaneously reverted to sinus rhythm after valve surgery without the maze procedure showed intermediate values for left atrial function.

The maze procedure is unlikely to restore atrial function in patients with mitral regurgitation and atrial fibrillation, even if sinus rhythm returns postoperatively. Because postoperative left atrial function in patients with sinus rhythm was similar to that in control patients, surgery should be considered for patients with severe mitral regurgitation while atrial function and sinus rhythm are maintained.

3. Effect of preoperative LV percent fibrosis on midterm outcomes after aortic valve replacement

The aim of this study was to investigate the effect of preoperative LV fibrosis on midterm outcomes after aortic valve replacement (AVR) and the relation between the plasma brain natriuretic peptide (BNP) concentration after AVR and the preoperative percent fibrosis.

Sixteen patients who underwent single AVR and left ventricular endomyocardial biopsy at the operation were enrolled in this study. The mean age at operation was 52.9±18.2 years. The total follow-up period was 118 patient-years with a mean follow-up period of 7.4±0.6 years. Serial echocardiographic examinations were performed before and after surgery in all patients. On the day of the final follow-up echocardiographic examination, the plasma BNP concentration was measured in 10 patients.

The preoperative percent LV fibrosis was 26.0%±9.2% (range, 10.8 % to 46.2%). The LV mass index (LVMI) decreased significantly from 201±92 to 143±79 g/m² and returned to the normal range after surgery in 9 of 16 patients. The LVMI in these 9 patients was less than 200 g/m² before the operation. The degree of preoperative LV fibrosis differed significantly between patients in whom the LVMI did (22.6%±7.0%) and did not (30.4%±10.3%, p=0.0456) normalize after surgery. The preoperative percent LV fibrosis was also strongly correlated with both the preoperative and postoperative LVMIs. This strong correlation indicated that the regression of LV hypertrophy after surgery depends on the progression of preoperative LV fibrosis, which is a decisive morphological alteration in LV remodeling. The BNP concentration 7.4±0.6 years after surgery was also strongly correlation with the preoperative percent LV fibrosis, being higher in patients with severe fibrosis.

A preoperative LVMI less than 200 g/m² can be a reliable predicator of reversible LV remodeling after valve replacement and should be taken into account when surgical intervention is considered.

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