

## Department of Cardiovascular Surgery

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### General Summary

The major achievements in our department included both clinical studies and experimental animal studies. The clinical studies include those establishing excellent surgical performance, investigating new techniques, and evaluating alterations in cardiac performance and long-term results after cardiac surgery. The experimental animal studies are performed to address clinical problems we are facing. A recent topic for adult surgery is the introduction of a new field — transcatheter aortic valve replacement — and we started preparing to perform such operations. We are also preparing to establish a left ventricular (LV) assist device program. We are also continuously performing several experimental studies with in-vivo models. The experimental projects include evaluation of hemodynamic performance during the Glenn and Fontan procedures, protection of the heart during cardiac arrest, and pulmonary valve function. The major activities are described below.

### Research Activities

#### *Experimental studies of “remote per-conditioning” as a new therapeutic strategy of myocardial protection*

An experimental study in an in-vivo piglet model was performed to test the hypothesis that ischemia/reperfusion (I/R)-induced biochemical damage and LV dysfunction can be reduced by “remote per-conditioning” (intermittent I/R of a remote organ before myocardial reperfusion). Fifteen piglets underwent 120 minutes of ischemia followed by 60 minutes of reperfusion while on cardiopulmonary bypass (CPB). In 5 of the piglets, remote ischemic preconditioning with 3 cycles of 30 seconds of I/R of a lower limb were applied before aortic unclamping, whereas the other piglets were not treated. Systolic and diastolic dysfunction of the LV associated with oxidant-induced biochemical injury was noted in the untreated group. In contrast, per-conditioning allowed significantly better LV functional recovery and less myocardial biochemical injury. This study in a piglet CPB model suggests that “remote per-conditioning” produces prompt myocardial functional recovery with less biochemical injury.

#### *Experimental studies of the severity of the pulmonary regurgitation fraction*

We investigated the impact of the physiological changes in pulmonary vasculature and right ventricular function on the hemodynamic severity of pulmonary regurgitation (PR) in a porcine model with severe pulmonary regurgitation.

Pulmonary vascular resistance (PVR) was changed by manipulating the PaCO<sub>2</sub> and by the inhalation of nitric oxide, and right ventricular (RV) function was manipulated with a dobutamine stress test to verify the effect of PVR and RV systolic function on the pulmonary regurgitant fraction (PRF). We found a significant positive correlation between PRF and PVR and a negative correlation between PRF and RV-segment shortening. This study demonstrates that PRF varies in proportion to changes in PVR and RV systolic function, which indicates that low PVR and high RV contractility are advantageous in reducing the severity of PR and the RV volume load after RV outflow tract reconstruction.

*Clinical studies of myocardial protection during pediatric heart surgery*

In infants with ventricular septal defect, atrioventricular septal defect, or other congenital malformations who underwent open heart surgery with various cardioplegic strategies, biochemical markers for myocardial injury (troponin T) and oxidative stress (8-iso-prostaglandin) were measured intraoperatively. This retrospective study confirmed the benefits of BCP with terminal warm BCP reperfusion (hot shot) over crystalloid cardioplegia on reperfusion-induced biochemical injury.

*Clinical studies of surgical outcomes of patients with univentricular heart*

1. Optimal timing of the bidirectional Glenn procedure to avoid interstage drop-out before the final Fontan procedure

The effects of age when the bidirectional Glenn (BDG) procedure is performed and of preoperative characteristics on the incidence of inadequate Fontan candidacy were analyzed with univariate/multivariate logistic regression in 49 patients who underwent the Glenn procedure (2001–2014). Impaired Fontan indication criteria were defined as pulmonary artery (PA) pressure (PAP)  $\geq 15$  mm Hg or peripheral vascular resistance (PVR) index  $\geq 3.0$  Wood units for the pulmonary factor and systemic ventricular end-diastolic pressure (EDP)  $\geq 12$  mm Hg for the ventricular factor. Multivariate regression analysis revealed that the presence of additional PA flow and the age when the BDG procedure was performed were independent predictors for impaired pulmonary and ventricular criteria, although preoperative hemodynamic variables and other anatomical subsets were not significant predictors on univariate regression. The incidence of impaired pulmonary and ventricular criteria was significantly lower in patients who underwent the BDG procedure before 12 months and 8 months respectively, than in older patients. In conclusion, the optimal timing of the BDG procedure is younger than 12 months for pulmonary risk factors and younger than 8 months for ventricular factors.

2. Optimal interval between the BDG procedure and the final Fontan procedure and the role of pulmonary vasodilator therapy

To evaluate the effects of the interval after the BDG procedure on the Fontan Risk Profile and the role of pulmonary vasodilator therapy, we analyzed changes in the Fontan Risk Profile (pulmonary or ventricular variables) during the interval between the BDG procedure and the Fontan procedure in 20 high-risk patients with complicated issues who underwent catheterization 2 or more times after the BDG procedure.

There was no significant change in PAP, PVR, EDP, or the PA index up to 12 to 24

months after BDG. However in high-risk patients who had been treated with bosentan or sildenafil, PAP and PVR decreased significantly 6 months after the BDG procedure. From these findings we conclude that: 1) during the interval after BDG of 3 to 24 months, PA index remained unchanged without progressive decreases, and 2) in high-risk patients with elevated PAP, pulmonary resistance, and EDP, a prolonged observation interval before the Fontan procedure associated with medication therapy (pulmonary vasodilator or angiotensin-converting enzyme inhibitor) has beneficial effects on risk factors.

### 3. Validity of extended indication of fenestration to borderline cases

Since 2001, the indications for fenestration at our institution have been extended to the lower-risk patients, who had at least 1 of the following criteria: PAP >15 mm Hg, peripheral resistance > 3.0 Wood units, PA index < 150 mm<sup>2</sup>/m<sup>2</sup> body surface area, systemic ventricular dysfunction, associated procedures, history of multiple open palliation procedures or Fontan take-down procedures, and use of a pulmonary vasodilator.

Consequently, of all patients undergoing the Fontan procedure, 18 patients underwent fenestration of 4 mm. Among these patients, 12 had spontaneous closure within 1 to 2 years after the Fontan procedure, whereas fenestration remained patent in the other 6 patients, including 4 patients with fenestration-dependent circulation. Postoperative catheterization revealed that patients with patent fenestration had higher central venous pressure (CVP) and lower cardiac index, and higher levels of type IV collagen, as a marker of liver fibrosis, even with fenestration, than did patients not undergoing fenestration or patients with spontaneous closure. On the basis of these findings we conclude that extension of the indications for fenestration to borderline cases appears to be an appropriate strategy to facilitate Fontan adaptation in low-risk cases leading to natural closure and to reduce morbidity and late complications in high-risk cases with ensured persistent patency.

### 4. Clinical study of the usefulness of the intraoperative Fontan simulation test under BDG circulation to predict Fontan outcome

As a strategy for high-risk surgical candidates, we proposed a novel method of intraoperative Fontan simulation testing under BDG circulation and applied this method to 20 high-risk Fontan candidates. Before CPB, the pulmonary flow-pressure (PAP and left atrial pressure [LAP]) relationship was analyzed by stepwise volume loading from a cannula, up to a preoperative pulmonary flow index of 2.5 L/min/m<sup>2</sup> body surface area, where effective PA flow is measured with a transit flow meter placed around the superior vena cava, with concomitant measurement of PAP and LAP. With the assumption that the minimum requirement of the cardiac index for successful Fontan during the acute phase is 2.5 L/min/m<sup>2</sup>, predicted CVP at Fontan completion was calculated as transpulmonary pressure gradient at a PA flow index of 2.5 plus baseline LAP before volume loading. We have shown a significant relationship between predicted CVP and CVP on the first postoperative day, suggesting a role for this index as a predictor of acute hemodynamic status.

### *Clinical study of adult cardiac surgery*

#### 1. Mitral valve repair in active infective endocarditis

For patients with mitral valve infective endocarditis (IE), mitral valve repair is preferred over mitral valve replacement. The objective of this study was to investigate the limitations of mitral valve repair for treating active IE by reviewing our recent operations for active IE. From January 2004 through August 2012, 24 patients with active IE underwent mitral valve surgery. The mean age of patients was  $60 \pm 16$  years. The active IE was classified into 4 types according to the severity of mitral valve destruction, and surgical treatments were selected for each: type I, vegetation with less destruction of leaflets and subvalvular apparatus, debridement by rubbing and ring annuloplasty; type II, 1 localized lesion, resection and suture; type III, 2 or more destructive lesions, resection and suture or patch augmentation with artificial chordae; and type IV, destruction extending over annular lesion, reconstruction of annuli with pericardial patch. We assessed the surgical outcomes of these patients with a focus on the validity of mitral valve repair for active IE. Of the 24 patients, 21 (87.5%) underwent mitral valve repair and 3 underwent mitral valve replacement. The surgical outcomes for both procedures were satisfactory. There were no late deaths and no recurrence of IE. The patients who underwent mitral valve replacement had type III IE (2 patients) or type IV IE (1 patient) and were the first in this cohort to be treated. In conclusion, mitral valve repair for active IE is a useful treatment for most cases and can be achieved with radical resection of infected portions and coverage of defects with a pericardial patch supported by artificial chordae. In cases of wide invasion or destruction, which should be resected, more complex procedures are needed. Therefore, early surgical intervention should be considered for successful mitral valve repair and for higher survival rates.

## 2. Use of mechanical aortic valves in patients older than 65 years

The first choice of aortic prosthesis in patients older than 65 years is a biological valve. However, new mechanical valves, which have a small annulus and larger effective orifice, have been implanted in elderly patients, but morbidity can be significant if the annulus is not enlarged. An increasing number of patients older than 60 years are receiving mechanical valves. The main reason mechanical valves are chosen, even for elderly patients, is chronic atrial fibrillation, which can be refractory to treatment and necessitate anticoagulation with warfarin. In this study, the validity of mechanical valve selection for patients older than 65 years was examined. Of patients aged 65 to 70 years, 32% strongly desired to receive a mechanical valve because of recent increases in mean life span. The 10% of patients older than 75 years elected mechanical valves because of the low invasiveness of their implantation when the calcified small annulus and ascending aorta are not enlarged. The other patients with structural valve deterioration (SVD) of a previous biological prostheses desired mechanical valves so that reoperation could be avoided. Our studies suggest: 1) the frequency of choosing mechanical valves in the young-old population has increased, 2) because the likelihood of postoperative treatment with warfarin is high, we have selected mechanical valves for patients with long-lasting atrial fibrillation undergoing multiple valve surgeries, and 3) we have implanted new small mechanical valves without annular enlargement in patients older than 80 years (most of whom are female) with a small annulus. However, the frequency of bleeding complications caused by treatment with warfarin has been low, and the mid-term results have been good. The validity of using mechanical valves for elderly patients should be

examined after long-term follow-up.

3. The role of a perioperative heart team composed of intensive care unit physicians and rehabilitation staff in dealing with the hemodialysis patients who underwent coronary artery bypass grafting

Recently, the number of patients receiving hemodialysis (HD) who undergo coronary artery bypass grafting has increased. In these patients, the risks of both surgical complications and morbidity is high. At our institution, a cooperative team has contributed to the recent excellent operative outcomes of these patients. The heart team decides on perioperative care after discussing treatment plans every morning. Because perioperative care takes place in the intensive care unit (ICU), the burden on the general wards has been relieved. We have introduced preoperative dental care, HD management during early admission, off-pump coronary artery bypass surgery, preoperative administration of amiodarone, the avoidance of using bilateral internal thoracic arteries, the control of blood glucose to less than 120 mg/ml, and the appropriate timing for the start of postoperative HD. After the transition from continuous to intermittent HD has been confirmed, patients are moved to the general wards. The ICU has 20 beds and is staffed by 8 ICU specialists. There are also 2 clinical engineers, 3 pharmacists, 60 nurses, and periodic rounds by the infection control team and dentists. Postoperative rehabilitation is started as soon as possible in the ICU. To reduce the burden on the general wards, in the ICU ventilatory support is provided via endotracheal intubation, and adrenergic agents are continuously infused. Care in the ICU and the cooperation of other co-medical staff have contributed greatly to the excellent postoperative outcomes, regardless of the complexities and severities of recent patient diseases.

4. The economic pitfalls of valvular operations for patients aged 80 years or older  
Operations for patients aged 80 years or older have become more common because of the recent growth of this segment of the population and the progression of medical technologies. Because an understanding of current economic problems of aged patients is important for discussing recent medical politics, we examined aged patients' medical charges of valvular operations. For aged patients, the cost of the diagnosis procedure combination (DPC) was higher than for adults in general, and their postoperative hospital stays were significantly longer. Perioperative care for aged patients are generally considered to be an excess burden for medical workers. On the contrary, the income of DPC showed no significant difference between young and old patients. So some additional fees must be needed for lower current estimation of the care of aged patients.

## Publications

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