

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 new fields, a transcatheter aortic valve replacement, and a left ventricular (LV) assist device program. We are preparing for them by having continuous meetings. 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. A new project we started this year is visualization of the cardiac conduction system in human heart specimens with high-resolution phase contrast computed tomographic (CT) imaging. 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: Variability of pulmonary regurgitation in proportion to pulmonary vascular resistance in a porcine model of total resection of the pulmonary valve

We investigated the effect 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 PaCO₂ 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.

Visualization of the cardiac conduction system in human heart specimens by the high-resolution phase contrast CT imaging

Introduction: The feasibility of visualization of the atrioventricular (AV) conduction axis in human whole heart specimens by means of a synchrotron radiation phase-contrast CT (PCCT) was tested.

Method. The PCCT images of 4 formalin-fixed autopsy specimens of normal whole hearts were collected in the Biomedical Imaging Centre, Super Photon Ring 8 Synchrotron Facility (Hyogo, Japan) with a PCCT system consisting of a Talbot interferometer. In the resliced PCCT images, low-density structures were distinctly recognized from surrounding tissue. Such structures were detected in the AV septum, penetrating the central fibrous body, extending on top of the interventricular septum, and bifurcating onto both sides of the ventricular septum. These structures were comparable with the AV conduction axis on pathological observation. From images sequenced, major subdivisions of the AV conduction axis were visualized within 3-dimensional heart structure.

Conclusion: The visualization of the AV conduction axis within whole heart specimens was feasible with the use of PCCT and verified by subsequent histological examination. Nondestructive evaluation of the AV conduction axis in cardiac specimens and its 3-dimensional representation may allow more comprehensive examination of the conduction tissue in congenital heart anomalies.

Clinical studies of surgical outcomes of patients with univentricular heart

1. Effect of pulmonary vasodilators on the pulmonary circulation in patients waiting for Fontan procedure following the Glenn operation

We retrospectively studied sequential changes of the pulmonary circulation and the effect of pulmonary vasodilators in patients waiting for Fontan procedure following the Glenn operation.

Thirty consecutive patients with single ventricle physiology were selected (double-outlet right ventricle, 11 patients; mitral atresia, 5 patients; tricuspid atresia, 4 patients; transposition of the great arteries, 4 patients; pulmonary atresia with intact ventricular septum, 2

patients; and other, 4 patients). The mean age of patients during the Glenn operation was 12 ± 9 months, the mean waiting period for the Fontan procedure was 16 ± 10 months, and the mean number of times the cardiac catheterization was performed was 2.8 ± 1.2 . One or more pulmonary vasodilators (sildenafil, 3 mg/kg/day; tadalafil, 1 mg/kg/day; bosentan, 3 mg/kg/day; and ambrisentan, 0.2 mg/kg/day) were administered to 15 patients starting from immediately after the Glenn operation. The other 15 patients served as a control group. In the control group, no significant change in pulmonary circulation or vascular features was observed while waiting for Fontan procedure. On the other hand, 6 to 12 months of pulmonary vasodilator therapy significantly decreased pulmonary artery (PA) pressure (PAP) by $85\% \pm 5\%$ and pulmonary resistance by $86\% \pm 7\%$ ($p < 0.05$). Our data suggest that treatment with pulmonary vasodilators for high-risk Fontan case might shorten the waiting period for Fontan procedure following Glenn operation by improving PAP and pulmonary resistance.

2. 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 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 PAP ≥ 15 mm Hg or PVR index ≥ 3.0 Wood units for the pulmonary factor and systemic ventricular end-diastolic pressure ≥ 12 mm Hg for the ventricular factor. Multivariate regression analysis revealed that the presence of additional PA flow and the age when the bidirectional Glenn 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 bidirectional Glenn procedure before 12 months and 8 months, respectively, than in older patients. In conclusion, the optimal timing of the bidirectional Glenn procedure is when the patient is younger than 12 months for pulmonary risk factors and younger than 8 months for ventricular 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 mm²/m² 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 pressures, lower cardiac indexes, 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.

Clinical study of adult cardiac surgery

1. Choice of aortic valve prostheses in the rapidly aging society

The current Japanese guidelines recommend the use of a tissue valve for aortic valve replacement (AVR) in patients older than 65 years. We have chosen an aortic prosthesis according to the guidelines after discussions with patients and family about various factors, such as age, comorbidities, surgical, and reoperation risk. Although the use of aortic tissue valves has markedly increased with the recent progression of the aging society, the detailed explanation of valve durability and anticoagulation therapy causes most patients to allow the type of valve to be chosen with the surgeon's experiences and preferences. Clinicians have often changed their ideas of which valve is best for patients aged 60 to 70 years, because patients live increasingly longer than the valves remain improvingly durable and will therefore require a new valve in 10 or 20 years. In the present study, we used propensity score matching to analyze the clinical outcomes after AVR in the recent rapidly aging society, focusing on the choice of valve for patients aged 60 to 70 years. From April 1995 through March 2014, 366 adult patients underwent single AVR or combined AVR/coronary artery bypass grafting. Of these patients, 127 (35%) received a mechanical valve and 239 (65%) received a tissue valve. A retrospective analysis of the entire population and the selected 124 patients aged 60 to 70 years was performed in comparison between the tissue valve and mechanical valve groups. Perioperative deaths occurred of 4 patients in the mechanical valve group (3.1%) and 8 patients in the tissue valve group (3.3%; $P = 0.92$). The 16-year overall survival rate was $87\% \pm 4\%$ for the mechanical valve group and $40\% \pm 29\%$ for the tissue valve group ($p = 0.220$). The rate of freedom from reoperation at 16 years was $98\% \pm 2\%$ for the mechanical valve group and $82\% \pm 9\%$ for the tissue valve group ($p = 0.005$). Propensity matching of the patients aged 60 to 70 years did not identify significant differences in the 16-year survival rate and freedom from reoperation between the tissue valve group and mechanical valve group. Both physicians and patients consider the possibility of reoperation in their 80s to be more serious than the risk of anticoagulant-related complications. The environment using tissue valves for patients aged 60 to 70 years has not been appropriate in the society that is rapidly aging and has an increased lifespan.

2. The fundamental technique of mitral valve repair in active infective endocarditis

Many institutions have reported good results with mitral valvuloplasty (MVP) for active infective endocarditis (AIE) in the mitral position. However, the reparability of mitral regurgitation due to AIE ranges from 35% to 81%. These reports have not shown the surgical strategies or the definition of AIE. The aim of this study was to examine the results of MVP for AIE during the last decade and to assess the surgical outcomes, with a focus on the validity of MVP for AIE. From January 2004 through December 2014, a series of 32 consecutive patients underwent MVP for AIE in the mitral position. The patients' mean age was 60 years. The infected portions were anterior mitral leaflet in 20 cases and posterior mitral leaflet in 27 cases. In 15 cases the infected lesions were in both the ante-

rior and posterior mitral leaflets. In 7 patients the infected area was in the annulus. Of these 32 patients, 27 underwent MVP and 5 underwent mitral regurgitation. The used techniques were of 5 types: leaflet resection, patch repair, artificial chordoplasty, edge-to-edge repair, and ring annuloplasty. For most cases of AIE, MVP is a useful treatment and can be achieved with radical resection of infected portions and coverage of defects with a pericardial patch supported by artificial chordae. For cases with wide invasion or destruction, which should be resected, more complex procedures are needed. Therefore, early surgical intervention should be considered for successful MVP and for higher survival rates.

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