

Department of Cardiovascular Surgery

Kazuhiro Hashimoto, *Professor*
Yuzuru Nakamura, *Professor*
Kei Tanaka, *Assistant Professor*
Ryuichi Nagahori, *Assistant Professor*
Michio Yositate, *Assistant Professor*

Kiyozo Morita, *Professor*
Yoshimasa Sakamoto, *Associate Professor*
Kouji Nomura, *Assistant Professor*
Yoshimasa Uno, *Assistant Professor*
Hirokuni Naganuma, *Assistant Professor*

General Summary

The main investigation in our department involved clinical study, evaluation of alterations in cardiac performance and long-term results after corrective surgery, and experimental studies to solve the clinical problems we are facing. Clinical investigations, including follow-up studies, of valvular and ischemic heart diseases were a main area of our clinical research, as were studies of complex congenital anomalies. Recent topic for adult surgery is mitral valve plasty in the cases of acute infective endocarditis. The recent increase in aortic aneurysms has continued and surgical strategy was established. We are also continuously performing several experimental studies with in vivo models. The experimental projects include protection of the heart during cardiac arrest and pulmonary valve function. The major activities are described below.

Research Activities

Experimental studies of congenital heart diseases: The effect of cardiopulmonary factors on the severity of pulmonary regurgitation in an acute swine model

The progression of pulmonary regurgitation after intracardiac repair for congenital heart defects requiring right ventricular (RV) outflow tract reconstruction results in the RV volume overload and subsequent RV dysfunction, contributing to poor morbidity and reoperation. We examined the effects of cardiopulmonary factors (RV systolic function [end-systolic elastance, E_{es}] and pulmonary vascular resistance index [PVRI]) on the severity of pulmonary regurgitation (PR) in an acute swine cardiopulmonary bypass (CPB) model. In 8 pigs (body weight, 14 ± 2 kg), an acute PR model was established with the use of CPB. The severity of PR (%PR) assessed with a Doppler flow meter (backward/forward flow area) was $40 \pm 4\%$ at the steady state after the operation. During the serial alterations of PVRI by manipulation of ventilation and NO inhalation, %PR increased in parallel with PVRI ($p < 0.01$ %PR versus PVRI). Furthermore, %PR was reduced by stepwise increases in RV E_{es} by dobutamine infusion. In conclusion, the hemodynamic effect of PR depends on the patient's cardiopulmonary status (i.e., RV function and pulmonary vasoconstriction) in addition to the status of pulmonary valve competence.

Experimental studies of new therapeutic strategies of cardiopulmonary protection during open-heart surgery

1. Reversal of oxidant-mediated biochemical injury and prompt functional recovery after prolonged single-dose crystalloid cardioplegic arrest in immature piglet heart by the

terminal warm-blood cardioplegia supplemented with a phosphodiesterase III inhibitor Terminal blood cardioplegia (TWBCP) alone provides insufficient benefits after prolonged ischemia and is associated with inevitable oxidant-mediated injury. To examine methods of avoiding oxidant-mediated myocardial reperfusion injury and of facilitating prompt functional recovery, we examined the effects of TWBCP supplemented with high-dose olprinone, a phosphodiesterase III inhibitor, which has the potential to reduce oxidant stress and calcium overload, after prolonged single-dose crystalloid cardioplegic arrest in a model of CPB in immature piglets. Fifteen piglets were subjected to 90 minutes of cardioplegic arrest on CPB, followed by 30 minutes of reperfusion. In group I, uncontrolled reperfusion was applied without receiving TWBCP; in group II, TWBCP was given; and in group III, TWBCP was supplemented with olprinone (3 $\mu\text{g}/\text{ml}$). Group III showed significant left ventricular (LV) performance recovery (Group I, 26.5% \pm 5.1%; group II, 42.9% \pm 10.8%; group III, 81.9% \pm 24.5%, $p < 0.01$ versus groups I and II), associated with significant reduction of troponin T and lipid peroxidation at the reperfusion phase. In groups III no piglets required electrical cardioversion. On the basis of this study, we conclude that TWBCP with olprinone reduces myocardial reperfusion injury by reducing oxidant-mediated lipid peroxidation and accelerates prompt and persistent LV functional recovery while suppressing reperfusion arrhythmia.

2. Effect of postconditioning: Experimental study using a piglet model of cardiovascular surgery on the reversal of myocardial stunning by ischemic postconditioning

Background: This study tested the hypothesis that myocardial damage induced by ischemia/reperfusion can be reduced by postconditioning at reperfusion.

Methods: Eighteen piglets were subjected to 90 minutes of ischemia followed by 60 minutes of reperfusion on CPB. In 12 of them, ischemic postconditioning strategies (6 cycles of 10 seconds of ischemia/reperfusion or 3 cycles of 30 seconds of ischemia/reperfusion) were applied before aortic unclamping, whereas the other 6 were not treated (control).

Results: In the LV, both systolic and diastolic dysfunction, associated with oxidant-induced biochemical injury, were noted in the control group. In contrast, postconditioning resulted in significantly better LV functional recovery and less myocardial biochemical injury.

Conclusion: Ischemic postconditioning during the early phase of reperfusion produces prompt myocardial functional recovery and inhibits biochemical injury in a piglet model of CPB.

Clinical studies of pediatric heart surgeries

1. Postoperative changes in coagulability and fibrinolytic function in Fontan circulation: Possibility of the conversion of anticoagulation therapy

There is still no consensus concerning the postoperative use and duration of treatment with warfarin as an anticoagulant in patients undergoing the Fontan procedure. We evaluated the changes in coagulability and fibrinolytic function after the surgery and try to use them as the indicator of anticoagulation therapy. Plasma levels of thrombin anti-thrombin-3 complex (TAT), as an index of coagulability, and $\alpha 2$ -plasmin inhibitor-plasmin complex (PIC), as an index of fibrinolytic function, were measured in 16 patients

undergoing the extracardiac Fontan procedure (mean age at operation, 4.2 years). Levels of both TAT and PIC remained higher than normal for 6 months after surgery, even in patients treated with warfarin. However, levels of TAT and PIC gradually decreased and had almost normalized by 12 months. On the basis of these results, we have replaced warfarin with an antiplatelet agent in these cases. Even after this change, plasma levels of TAT and PIC have remained normal, and no patients have shown thromboembolic events on echocardiography. This study suggests that patients undergoing the Fontan procedure should receive anticoagulation therapy with warfarin for the first year after surgery because of their activated status of coagulability. However, warfarin can be replaced with an antiplatelet agent 12 months after surgery for patients with normal levels of TAT and PIC and no major complications.

2. Effects of oral pulmonary vasodilators (sildenafil and bosentan) in high-risk candidates for the Fontan procedure after the bidirectional Glenn operation

We have retrospectively analyzed the effects of treatment with oral pulmonary vasodilators (sildenafil and bosentan) on the hemodynamic risk profile (pulmonary arterial pressure [PAP], pulmonary vascular resistance: pulmonary resistance [Rp] and PA index) in 8 high-risk candidates for the Fontan procedure and 10 untreated control patients.

In the treatment group, 8 patients who underwent bidirectional Glenn (BDG) operation, significant reductions in Rp and PAP were noted 6 and 12 months after the operation, whereas no changes were demonstrated in the control group. This study suggests that treatment with oral pulmonary vasodilators (sildenafil and bosentan) can reduce pulmonary risk factors in candidates for the Fontan procedure.

3. Intraoperative evaluation of pulmonary flow reserve capacity and a new method to predict post-Fontan hemodynamic status

In 12 patients, in whom the staged Fontan procedure was indicated after the BDG operation, we measured superior vena cava flow, which is equivalent to PA flow in BDG physiology, by means of a transit-flow meter intraoperatively. Measurement of PA flow and pulmonary vascular resistance, incorporated with serial volume loading, allows pulmonary vascular reserve capacity to be assessed in response to an increase in pulmonary flow to simulate Fontan circulation. The pulmonary vascular reserve capacity, assessed by the percent reduction in Rp in response to increased pulmonary flow, was revealed to be a strong indicator of post-Fontan outcome and a final central venous pressure (CVP) with Fontan circulation. In 8 patients who had undergone the Fontan procedure, there was significant relationship between the actual CVP and the CVP predicted by means of intraoperative simulation.

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

The surgical outcomes and long-term results of the Ross operation were reviewed in 35 patients who undergone the Ross procedure from 1995 through 2008. Autograft function was assessed with periodic echocardiographic evaluation for up to 14 years after the operation. There were no operative or acute deaths or late reoperation for autograft regurgitation (freedom from reoperation for autograft failure: 87% after 14 years). The durability of the implanted pulmonary autograft valve was excellent, especially in children and in patients with preoperative aortic stenosis.

Clinical study of adult cardiac surgery

1. Valve disease

1) Increase of re-do surgery~for safer operations

1)-1. *Risk factor*: Recently, the number of re-do surgeries have increased because of the increased number of elderly patients. Most re-do cases involve several severely diseased valves, and the mean interval after the first operation is 19.6 ± 9.5 years. Many patients have cardiac cachexia because of the chronic right heart failure. Moreover, congestive liver damage and splenic hyperactivity cause platelet deficiencies that affect the amount of blood loss during the operation. Although the number of redo surgeries, the amount of blood loss, operation time, and cardiopulmonary bypass time were not risk factors in the our redo surgeries, but renal and liver dysfunction were risk factors for operative mortality.

1)-2. *Surgical approach*: Before sternotomy, DC pads are placed to treat possible arrhythmias, and the femoral artery and vein are kept for cardiopulmonary bypass. The key to dissecting adhesions is to avoid injuring the heart and vessels. To keep from injuries, sternotomy must be done while the previously used wires are pulled upward. It is important to take care of dissecting the adhesion of prosthetic stents, injuries of the coronary orifice, and the left ventricular posterior wall when the old prostheses in the aortic and mitral positions are removed. After removal of the old prostheses, a new annulus is constructed with a pericardial Xenomedica patch if the annulus is defective. We use On-X or MOSAIC valves in the tricuspid position.

2) Valve operation for patients aged older than 80 years

Increase of the valve surgeries of the elderly patients: Reflecting the recent aging society, the number of valve operation in our department has been increased in recent years which is close to 10% of the total valve operations. We have to be more careful to choose the adequate surgical approach, thinking over the patient's complications and QOL before operation. Most of valve operations are associated with aortic valve replacements, using bioprosthetic valves and the results are satisfactory. The operative risk is around 5% and the surgical indication should be decided with the preoperative condition and risk scores.

3) Aortic valve replacement in elderly patients

Effect of patient-prosthesis mismatch: The frequency of patient-prosthesis mismatch (PPM) was around 12%, which was higher than expected. PPM did not affect survival, and moderate PPM was tolerable. Our exponential curve was different from the original curve that was constructed from the data of 4 different prostheses and defined the criteria of PPM. The mean pressure gradient of the stented bioprosthetic valve demonstrated a gentler slope and a smaller effective orifice area indexed with body surface area compared with the exponential curve described by Pibarot and Dumesnil¹⁾. The practical implications of these findings include the necessity to reconsider the hemodynamic performance of each prosthesis when seeking to define PPM, so as to avoid residual significant transvalvular pressure gradient and higher rates of morbidity and mortality.

A) Hemodynamic and clinical impact of prosthesis-patient mismatch in the aortic valve position and its prevention. Pibarot P, Dumesnil JG, J Am Coll Cardiol 2000; 36:1131-41.

2. Ischemic heart disease

1) Perioperative management of recent cardiac surgeries

1)-1. *Perioperative management*: It is important to establish specialized medical teams to improve surgical results in an aging society that includes patients with serious complications, such as diabetes and hemodialysis.

Infection: The oral cavity is routinely checked by dentists. Cefazolin sodium is administered every 3 hours intraoperatively and for 4 days after the operation. We meet with the infection control team once a week.

Diabetes: Blood glucose levels are controlled with the insulin scale before surgery, and continuous insulin infusion maintains postoperative blood glucose levels at less than 180 mg/dl. We routinely consult with diabetes specialists doctor about the control of postoperative blood glucose.

1)-2. *The intensive care unit system*: In our institution, 8 intensive care unit (ICU) specialists and specialists in nephrology, infection control, and other fields help care for patients after surgery in our 20-bed ICU. The cooperative team has contributed to the shortening of the mean ICU stay even though the number of patients with serious comorbidities has increased.

Rehabilitation: In the ICU, a cardiovascular physiotherapist begins postoperative rehabilitation.

3. Thoracic aneurysm

1) Preventing cerebrovascular complications in aortic arch replacement

The first choice for an aortic infusion line is an ascending aorta without calcification. If there is atherosclerosis, we select an axillary artery. Moreover, we have cannulated atheromatous branches of the aortic arch which have sufficient backflow, achieved by means of selective cerebral perfusion, followed by initial retrograde cerebral perfusion. To prevent the complications of cerebral infarction and air embolism, retrograde cerebral perfusion is a safe and simple method of brain protection.

Publications

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