

## **Combined heart and kidney transplantation: report of two cases.**

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### **Abstract**

**Background:** Combined Heart and Kidney Transplantation (CHKT) has become an accepted therapy for patients with coexisting heart and renal failure. Because only a few cases can be observed in the clinical practice, there is no guideline for this treatment and a lack of long-term follow-up.

**Study design:** For a reasonable and safe application of CHKT in the clinical practice, we analysed the follow-up data of two patients who underwent combined heart and kidney transplantation in our hospital.

**Measures and outcomes:** We described two male patients with end-stage cardiac and renal disease who underwent CHKT. Secondary allograft kidney transplantation was performed for one patient due to the dysfunction of the transplanted kidney and long-term follow-up was carried out.

**Results:** Two patients had lived 145 months and 13 months respectively after surgery. Factors such as the surgical procedure, perioperative vasoactive drug application, selection of immunosuppressants, Continuous Renal Replacement Therapy (CRRT) support at the time of severe right heart dysfunction, application of broad-spectrum antibiotics and antiviral drugs, etc. affected the outcomes after transplantation.

**Conclusions:** CHKT is an effective method for the end-stage heart and renal failure. Postoperative rejection monitoring is critical and secondary kidney transplantation is the best way for the renal failure after combined heart and kidney transplantation.

**Keywords:** Combined heart and kidney transplantation, Secondary kidney transplantation, Graft rejection.

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### **Introduction**

Combined heart transplantation can be an option for selected patients with failure in dual vital organs. Combined Heart and Kidney Transplantation (CHKT) is a feasible option for patients suffering from end-stage heart and kidney disease and has excellent outcomes [1]. Although there are no standardized criteria for these combined procedures, a number of individual case studies and several series from single centers and registry data show a steady increase of CHKT [2]. However, many factors affect the outcomes after transplantation, and lung infection and graft rejection are the major factors. Because only a few cases can be observed in the clinical practice, there is no guideline for this treatment. For a reasonable and safe application of CHKT in the clinical practice, we analysed the follow-up data of two patients who underwent combined heart and kidney transplantation in our hospital.

### **Case Reports**

#### **Case one**

A 46-year-old man was admitted to our hospital on February 16, 2001 with repeated oliguria for 4 years and shortness of breath and chest tightness for 2 years, which became

aggravated before 2 weeks. The baseline information was shown in Table 1. The patient was diagnosed with end-stage dilated cardiomyopathy associated with idiopathic glomerulosclerosis (uremia) and underwent combined heart and kidney transplantation on April 27, 2001. The heart and kidney were harvested from a brain-death donor. Orthotopic heart transplantation (Lower and Shumway technique) was performed under extracorporeal circulation. Intraoperative myocardial protection was carried out by continuous retrograde infusion of warm blood through the coronary sinus. Spontaneous return of circulation took place after surgery. The blood pressure of 100 to 120/60 to 80 mmHg was maintained by small doses of vasoactive drugs. The heart rate was 100-110/min and the level of CVP was 15-18 cmH<sub>2</sub>O. The extracorporeal circulation was stopped when the hemodynamic stability was obtained basically. Kidney transplantation was then carried out in a conventional way *via* a left inferior abdominal incision. The wounds in the chest and abdomen were closed. Urination began several minutes after kidney transplantation. The maximum urine output reached 1500 ml/h. Close monitoring was carried out. Crystalloid and colloidal solutions were used to maintain the water, electrolyte and acid-base balance. Right heart dysfunction once occurred after surgery. CVP ranged between 25-30 cmH<sub>2</sub>O. The heart function improved after diuresis and dilation of pulmonary

capillaries. Endomyocardial Biopsy (EMB) was carried out 10 days, 3 weeks, 6 weeks and 16 months after surgery. The results ranged between grades 0 and 1A according to the International Society for Heart and Lung Transplantation (ISHLA) guideline (The last one was grade 0). There were no severe acute rejection and severe infection. The patient was discharged 49 days after surgery and returned to normal work soon. The heart and kidney functions were normal and the quality of life was good. But the patient felt fatigue, chest tightness and shortness of breath again 20 months after surgery (January 2003). The 24 h urine output had been only 700 ml for several days and the patient was admitted to our hospital again. Physical examination showed that the vital signs were stable and there was no rale. The heart rate was 84/min. No arrhythmia or pathological murmur was heard. The blood pressure was 116/85 mmHg. The abdomen was soft and no lower-extremity edema was observed. Pulse therapy using methylprednisolone (500 mg iv qd  $\times$  3) and OKT3 (5 mg iv gtt qd  $\times$  12) was carried out and the patient was discharged after all indicators became normal. Immunotherapy using FK506, MMF, steroid and daclizumab was carried out then. The creatinine level was still very relatively high after that and it even reached 200-250  $\mu$ mol in spite of adjusting the dose of immunizing agents. In November 2009, the creatinine level was 717  $\mu$ mol/L, the BUN level was 28.1 mmol/L and the endogenous creatinine clearance was 8.79 ml/min. The patient felt dizziness, chest tightness and shortness of breath and admitted to our hospital again. The patient underwent hemodialysis three times a week and the creatinine level decreased slightly. Moderate amount of bilateral pleural effusion was observed, which was resolved by several times of thoracentesis and adjusting the hemodialysis. Negative result was shown in the *Mycobacterium tuberculosis* antibody test and no cancer cell was found in the pleural fluid. On January 27, 2010, nine years after the combined surgery, the patient underwent secondary kidney transplantation. The patient has lived and worked with normal heart and kidney functions for more than 36 months after that.

## Case 2

A 51-year-old man was admitted to our hospital because of chest tightness after activities for 3 years and oliguria for 1 year. The patient was diagnosed with dilated cardiomyopathy, end-stage chronic renal failure, stage 2 hypertension, and type 2 diabetes and underwent combined heart and kidney transplantation on December 31, 2011. The heart and kidney were from a donor died in a traffic accident. Intraoperative myocardial protection was carried out by continuous retrograde infusion of oxygenated blood through the coronary sinus. Spontaneous return of circulation took place after surgery. The extracorporeal circulation was stopped when the hemodynamic stability was obtained by a small dose of vasoactive drugs. Kidney transplantation was then carried out in a conventional way *via* a left inferior abdominal incision. The wounds in the chest and abdomen were closed routinely. Postoperative immunosuppressive therapy was carried out using Daclizumab-induced cyclosporin A, MMF and steroid. After surgery, the patient had severe right ventricular dysfunction and required large doses of adrenaline (a maximum dose of 0.4 to 0.7 mg/h) and other vasoactive drugs to maintain a heart rate of 110 bpm. The blood pressure was 140/80-95 mmHg, CVP was 18-24 cmH<sub>2</sub>O. However, the urine volume was still 30-50 ml/h. The reason was considered to be application of large doses of vasoactive drugs for the donor during rescue. In order to protect the transplanted heart function, short-term Continuous Renal Replacement Therapy (CRRT) was carried out. The patient gradually became sensitive to the dopamine, dobutamine and epinephrine after CRRT and the amount of urination gradually became normal. Broad-spectrum antibiotics were used after surgery to prevent infection. Preventive antiviral and anti-fungal medications were carried out 10 days after surgery. The patient was discharged 31 days after surgery, and the heart and kidney functions were normal 13 months after surgery.

**Table 1.** Baseline and post-operation information of case one.

	At admission	Post-operation	20 months after surgery	Before secondary kidney transplantation	Secondary kidney transplantation
Date	February 16, 2001		January 2003	January 2007- November 2009	January 27, 2010
Laboratory tests					
Serum creatinine, $\mu$ mol/L	283.7		180	717	
Creatinine clearance, ml/min				8.79	
Blood urea nitrogen, mmol/L	8.52		13.7	28.1	
Other examination					
Echocardiography	Significantly expanded atrio-ventricular cavity; Left ventricular ejection fraction 27%				

Cardiac catheterization	Pulmonary artery pressure ranged from 36 to 38 mmHg; The pulmonary vascular resistance: 2.19 Wood units			
Renal biopsy	Glomerulosclerosis and focal fibrinoid necrosis with inflammatory cell infiltration, focal tubular atrophy with lymphocytic infiltration	Acute tubulointerstitial rejection	Chronic allograft nephropathy (severe) with global sclerosis	
Endomyocardial biopsy	Ranged between grades 0 and 1A		Grades 0-1A	
Treatment				
Controlling of blood pressure	Enalapril Maleate and Norvasc			
Immunosuppressive therapy	Daclizumab-induced cyclosporin A, Mycophenolate Mofetil (MMF) and steroid	Tacrolimus (FK506), steroid and daclizumab	MMF, and	FK506, steroid and daclizumab
Antibiotics	Short-term broad-spectrum antibiotics; Diflucan for the infection of <i>Candida albicans</i> in the urine culture 10 days after surgery; Three weeks of Ganciclovir infusion for positive CMV IgM 14 days after surgery without any clinical symptoms			
Hemodialysis	No	No	Hemodialysis three times a week since November 2009	Stopped after secondary kidney transplantation

## Discussion

Combined Heart and Kidney Transplantation (CHKT) is a feasible option for the treatment of coexisting end-stage heart and renal failure. The outcome is excellent and the simultaneous homologous transplantation can save medical cost, and it has significant advantages in the aspect of anti-rejection [3]. However, different from the single heart or kidney transplantation, there are more factors affecting the outcome of combined heart and kidney transplantation. The transplanted organs should be protected more carefully during the perioperative period. It is very important to resolve the contradiction between the perioperative right ventricular dysfunction and treatment of the transplanted kidney. In addition, the pulmonary infection and graft rejection should be prevented. The long-term outcome will improve significantly if all the aspects mentioned above are handled correctly. The long-term immunosuppressive therapy after combined heart and kidney transplantation may cause dysfunction of the transplanted kidney, which affects the quality of life. Hence, hemodialysis is an essential choice for stabilizing the internal environment, and secondary kidney transplantation is the best option for life-saving.

Surgical procedure of the combined heart and kidney transplantation Kidney transplantation can be performed immediately after heart transplantation or after a while [4-6]. There is no significant difference between two methods in the recovery of kidney function. The heart transplantation and the kidney transplantation were performed simultaneously for our two cases. This method can shorten the cold ischemia time of the transplanted kidney, avoid repeated anesthesia, and

simplify the surgical process. Its disadvantage is that the recovery of kidney function can be delayed or even kidney dysfunction may occur in case of donor heart dysfunction due to hemodynamic instability of the ischemic donor kidney, low perfusion pressure and subsequent application of a large dose of vasoconstriction drugs. In the case 2, severe right heart failure and kidney dysfunction occurred. The possible reason is that a large dose of vasoactive drugs were used for the donor during cardiopulmonary resuscitation. Thereby, continuous renal replacement therapy was required in this case.

Perioperative treatment of the combined heart and kidney transplantation is similar to that of the heart transplantation. Sufficient preoperative examination should be carried out before transplantation for detecting the heart and kidney functions, and renal dialysis can be performed if necessary. The body weight and size of the donor should be similar to those of the recipient, and ABO blood types should be compatible with each other. Human Leukocyte Antigen (HLA) matching should be performed retrospectively only because it may lead to extension of the cold ischemia time in the donor organ [7]. Besides paying enough attention to the management of the respiratory tract, anti-rejection, anti-infection, nutritional support and quarantine monitoring, management of the circulatory system should be strengthened to resolve the contradiction between the heart and kidneys treatments. Factors including the warm ischemia, cold ischemia, surgery, anesthesia, loss of nervous system regulation, etc. may affect the donor heart, and the vascular system of the recipient cannot adapt to that of the donor immediately after the heart transplantation. Hence, establishment of a new balance

requires a certain length of time, and low cardiac output, right heart failure, high blood pressure, etc. occur after surgery. It requires that the amount of fluid input and the blood pressure should be controlled effectively. Recovery of kidney function depends on the adequate perfusion pressure and amount. The function of the transplanted kidney is not able to recover at once, which leads to water and electrolyte balance disorder, increase the burden on the heart. Hence, the circulatory function, kidney function, fluid intake and output, etc. should be monitored carefully and renal replacement therapy should be carried out if necessary. We applied diuretic and inotropic drugs for our CHKT patients in the current study, controlled the fluid intake and output, and maintained the water, electrolyte and acid-base balance. As a result, the heart and kidney functions recovered quickly and it is consistent with other reports [8,9]. CRRT is the best choice of kidney support after heart transplantation. Its prominent advantages include the slowness, continuity, stability, high degree of automation, etc. and it can safely, reliably and stably substitute the kidney. The secondary kidney transplantation after the combined heart and kidney transplantation can be performed like the ordinary kidney transplantation because the heart function is excellent. The principle is to protect the two organs at the same time and maintain the hemodynamic stability and satisfactory perfusion pressure.

Immunosuppressive therapy of the combined heart and kidney transplantation should be in accordance with that of the heart transplantation. It is composed of induction therapy, maintenance therapy and treatment of acute rejection. The principle includes preventive medication, drug combination, appropriate drug selection and early medication. The commonly used drugs include corticosteroids, calcineurin inhibitors, and proliferation inhibitors and anti-lymphocyte antibodies. These drugs are used in various processes of the rejection, such as T cell activation, cytokine release, and immune cell proliferation, to inhibit the immune system. Cyclosporine A-based triple immunosuppressive therapy (cyclosporine A, azathioprine and steroids) is a generally used method. Application of cyclosporine A should be stopped or delayed in cases with early renal failure, and it can be replaced by anti-thymocyte globulin or other drugs. Recently, there is a tendency to use the FK506, MMF and monoclonal anti-lymphocyte globulin, anti-thymocyte globulin for the induction therapy. Monitoring mainly depend on the clinical symptoms and signs, electrocardiogram, echocardiography, detection of the peripheral blood T lymphocytes, X-ray images, Endomyocardial Biopsy (EMB) and biopsy of the transplanted kidney. The acute rejection is mainly treated by the methylprednisolone pulse therapy. In a few severe cases, total lymphoid irradiation or plasma exchange can be applied. We applied Zenapax-induced triple immunosuppressive therapy (cyclosporine A, mycophenolate mofetil and corticosteroids) for the first case. It not only reduced the side effects of the drugs and prevented the occurrence of severe infection, but also effectively controlled the acute rejection. The patient's heart and kidney functions were excellent 30 months after surgery. However, acute rejection occurred after that and pulse

therapy using OKT3 and methylprednisolone was carried out. After all indicators became normal, FK506, MMF and steroids were used again for anti-rejection therapy. The renal function decreased gradually, and renal failure happened. It might be caused by the renal toxicity of cyclosporine A or the chronic renal allograft rejection. Secondary surgery was performed and anti-rejection therapy using FK506, MMF, Zenapax and steroids was carried out again. The heart and kidney functions were normal during 36 months of the follow-up period. In the second case, 20 mg basiliximab-induced FK506+MMF+steroid anti-immune therapy was used after combined heart and kidney transplantation. The patient recovered excellently after surgery, and the heart and kidney functions have been normal for 12 months until now. The incidence of rejection is lower after the combined heart and kidney transplantation compared to the single organ transplantation, and its postoperative survival rates of the transplanted organs and the patients are similar to those of the single heart transplantation [10,11]. Combi-effect may be the reason of the body tolerating the transplanted heart. However, rejection may occur independently in the heart and kidney [12]. In one of our two cases, late-stage rejection of the transplanted kidney occurred, and the possible reason was the insufficient anti-rejection therapy. The late-stage dysfunction of the transplanted kidney also might be related to the CsA-induced renal damage and the application of calcium antagonists for controlling hypertension. The calcium antagonists might aggravate the CsA-induced irreversible renal damage. However, the exact mechanism should be further studied. Therefore, the blood CsA concentration, the liver and kidney functions, and the changes in the peripheral blood should regularly be monitored. The drugs and their doses should be adjusted in time according to the blood drug concentration and the states of rejection and side effects. The effect of other drugs on the transplanted kidney and the blood drug concentration of immunosuppressant should be observed carefully.

Complications and their prevention besides the acute rejection, infection is a main complication and a reason of death after the combined heart and kidney transplantation. Therefore, its prevention and early diagnosis are critical. Postoperative short-term broad spectrum antibiotics, such as Sulperazone, Tienam, etc., can be used according to the blood culture and susceptibility results. When the duration of using broad-spectrum antibiotics is relatively long, antiviral and antifungal drugs should be used to prevent the superinfection. Other complications include hypertension, chronic liver disease, hyperlipidemia, diabetes and malignancy. In the first case, *Candida albicans* was detected in the urine culture 10 days after surgery and Diflucan was used to control the fungal infection effectively. 14 days after surgery, the patient was found to be cytomegalovirus IgM positive and intravenous ganciclovir therapy was applied for 3 weeks until the cytomegalovirus antibody test became negative and there were no clinical signs of infection. In the second case, anti-infection therapy using tazocin was applied after surgery. 10 days later, acinetobacter calcium acetate (RIV weakly positive) was detected from the sputum culture and meropenem was used

instead of tazocin. Moreover, candida and ganciclovir were used to prevent the secondary infection. And the outcomes were satisfactory.

Summing up, the combined heart and kidney transplantation is an effective method for the end-stage heart failure and renal failure if it is appropriately applied. For this surgical procedure, contradiction between the heart transplantation and the kidney transplantation should be resolved properly, the rejection should be controlled properly, the heart and kidney functions should be monitored closely after surgery, the dose of immunosuppressants should be adjusted in time, and enough attention should be paid to the effects of other drugs on the concentration of immunosuppressants. Moreover, when the renal failure of the transplanted kidney occurs, secondary kidney transplantation should be performed and the outcome will be better than that of the hemodialysis [13,14]. It has been reported that the survival rate of patients undergoing secondary kidney transplantation is lower than that of patients undergoing combined heart and kidney transplantation only [15]. However, it should be further verified in the clinical study.

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