Experimental Orthotopic Heart and Bilateral Lung Transplantation Completed Without Cardiopulmonary Bypass*

Masaki Otaki, MD; Takehiro Inoue, MD; Terufumi Matsumoto, MD; Hitoshi Kitayama, MD; and Hidetaka Oku, MD

Introduction: Most experimental studies of orthotopic heart and lung graft failure are complicated by an inability to eliminate the rejection-specific inflammatory mediator from the cardiopulmonary bypass.

Methods: The following model was developed in our laboratory to investigate the feasibility of performing an orthotopic heart and bilateral lung transplantation without performing a cardiopulmonary bypass. Nineteen transplants were attempted using 19 pairs of mongrel dogs. The recipient dog (mean weight, 23 kg) was anesthetized, and the ascending aorta, the superior vena cava (SVC), the inferior vena cava (IVC), and the main bronchus were dissected. Then, the donor dog (mean weight, 20 kg) was anesthetized, and the heart and lung block was prepared and explanted from the chest under cardioplegic arrest. A Gore-tex shunt (W. L. Gore; Flagstaff, AZ) was placed side-to-side between the recipient IVC and SVC, and then the donor right atrium was anastomosed to the Gore-tex shunt. The donor ascending aorta was anastomosed to the recipient ascending aorta with a partial clamp. On completion of these anastomoses, the donor heart was reperfused by the recipient heart and allowed to beat. When hemodynamic conditions were stable with double hearts, the recipient SVC and IVC were ligated just proximal to the venous anastomosis and the recipient aorta was ligated proximal to the anastomotic site. The recipient trachea was anastomosed to the donor trachea with an end-to-end anastomosis. Finally, the recipient heart and lungs were removed from the chest and the sternum was closed.

Results: Four of the 19 transplants failed. Three died due to left ventricular dysfunction, and one died due to bleeding. Mean (± SD) ischemic time was 67 ± 11 min with a mean (± SD) anastomotic time of 54 ± 12 min. The 15 survivors were hemodynamically stable with double hearts, the recipient SVC and IVC were ligated just proximal to the venous anastomosis and the recipient aorta was ligated proximal to the anastomotic site. The recipient trachea was anastomosed to the donor trachea with an end-to-end anastomosis. Finally, the recipient heart and lungs were removed from the chest and the sternum was closed.

Conclusions: On the basis of our experiences, the experimental model of orthotopic heart and bilateral lung transplantation completed “off pump” can be technically feasible without the loss of cardiac and pulmonary functions.

Key words: experimental orthotopic transplantation; heart and lung transplantation; off pump

Abbreviations: IVC = inferior vena cava; NS = not significant; SVC = superior vena cava

The earliest experimental attempts at orthotopic replacement of the heart and lungs in combination were performed by Demikhov in the 1940s without the aid of cardiopulmonary bypass, and accomplishments of his study were reported in 1962.1

Since this report was published, several experimental methods have been attempted using cardiopulmonary bypass,2-4 but they have not been developed because of the disadvantages associated with cardiopulmonary bypass. Some of these disadvantages are related to disturbances in coagulation,
vascular tone, capillary permeability, fluid balance, and organ function, especially lung. Therefore, easily reproducible canine models of orthotopic heart and lung transplantation with good survival have been sought.

The purposes of our set of experiments were the following: (1) to develop a new technique of orthotopic heart and lung transplantation; (2) to assess the feasibility in performing transplantation without using cardiopulmonary bypass; and (3) to evaluate cardiac performances before and after heart and lung transplantation with the echocardiogram.

**MATERIALS AND METHODS**

Our experimental procedure involved 19 pairs of mongrel dogs, with the donor weight slightly greater than that of the recipient. The mean (± SD) weight was 23.2 ± 3.6 kg in the donor dogs and 20.3 ± 3.2 kg in the recipients.

**Experimental Procedures**

**Donor Animal:** The donor animal was anesthetized, intubated, and ventilated, and arterial monitors were placed. The standard median sternotomy was performed, and the great vessels were dissected along with the main bronchus and trachea. The carotid, vertebral, and subclavian vessels were dissected, and the pericardium was opened. A perfusion catheter was placed in the carotid artery. A two-dimensional echocardiogram of the donor heart was obtained, and the inferior vena cava (IVC) and the superior vena cava (SVC) were clamped along the aorta. The trachea was subsequently clamped and transected, and the right atrium was opened. The heart was then flushed with 400 mL of cold crystalloid cardioplegia, and the donor heart and lung were removed *en bloc*. This block was then transferred to cold storage, and the vessels were prepared for subsequent transplantation.

**Recipient Animal:** The recipient animal was simultaneously anesthetized with sodium pentobarbital and intubated and ventilated, and arterial monitors were placed. The standard median sternotomy in the recipient dog was performed, and the great vessels and trachea were dissected from the chest cavity. In our earlier series of animal heart and lung transplantation (unpublished data), the direct end-to-side anastomoses between the donor and recipient IVC and SVC was performed, but due to increased tension on the anastomoses, the venous return to the donor heart was considered inadequate. In this series of transplantation, a Gore-tex shunt (W. L. Gore; Flagstaff, AZ) was placed side-to-side between the recipient IVC and SVC, and then the donor right atrium was anastomosed to the Gore-tex shunt.

**Anastomoses:** An end-to-side Gore-tex shunt to the recipient IVC was anastomosed together followed by an end-to-side Gore-tex shunt to the recipient SVC. Then, the donor right atrium was anastomosed to an opening in the Gore-tex graft (Fig 1). An arterial connection was created by anastomosing the donor descending aorta and the recipient ascending aorta using partial occlusion of the recipient vessel (Fig 2).

**Following Anastomoses:** Air was removed from the donor heart. All clamps were removed, and the donor heart was allowed to fill with blood from the recipient heart. The donor trachea was attached to a ventilator. The donor heart was massaged and defibrillated if necessary until it could beat on its own. Inotropic support including small doses of dopamine (2 to 3 μg/kg/min) was used as needed. The donor lungs were ventilated using a second ventilator.

**Parallel Circuits:** Double hearts and double bilateral lungs were created, and the simultaneous function of both hearts and lungs was demonstrated. The grafts were essentially piggy-backed, with the recipient heart initially responsible for systemic perfusion. An example of a pressure tracing showing donor-recipient combined heart beats is shown in Figure 3.

**Transfer Venous Return From Recipient to Donor:** Venous return was gradually transferred to the donor heart by progressive ligation of the recipient vena cavae, with systemic oxygenation through the donor lungs. The recipient aorta was then ligated proximal to the anastomosis, rendering the circulation...
entirely dependent on the donor graft. When the donor and recipient trachea were anastomosed, the donor lung was ventilated with the trachea tube intubating through the recipient to the donor trachea. The trachea anastomosis was completed, rendering oxygenation entirely dependent on the donor lung (Fig 4). After complete stability, the recipient heart and lungs were resected, leaving only the orthotopic donor graft. Hemodynamic parameters, echocardiograms, and blood gas information were obtained every 30 min over the next 6 h. When the animals were hemodynamically stable, the sternotomy was repaired.

This study was designed to clarify the technical feasibility of performing heart and lung transplantation “off pump” and to obtain the acute hemodynamic data. Therefore, an aseptic operative field was prepared, and antibiotics and immunosuppressive drugs were not administered. Records of all hemodynamic data were continued with the intensive care of fluid balance and ventilation for 6 h after transplantation. After 6 h, this study was automatically continued for 10 h after grafting with the simple monitor of the aortic pressure, and then all of the animals were killed.

Results were interpreted with regard to the possibility or technical feasibility of the procedure. Criteria for short-term survivorship were based on the following: (1) chest closed; (2) mean systemic pressure > 75 mm Hg without inotropes or with minimal doses of inotropes (dopamine, 2 to 3 μg/kg/min); and (3) PaO2 > 85 mm Hg on room air.

The Guide for the Care and Use of Laboratory Animals followed carefully during these experiments.5

RESULTS

Nineteen transplantations were performed in this series. All donor hearts were weaned from the recipient heart. Four dogs were weaned, but three died within 2 h after transplantation due to left ventricular dysfunction and one died due to bleeding. These four deaths were not related to pulmonary dysfunction. The mean (± SD) ischemic time of the donor heart and lungs was 67 ± 11 min, and the mean (± SD) anastomotic time between venous and arterial correction was 54 ± 12 min.

Fifteen animals were hemodynamically stable 6 h after grafting without inotropic support or with a minimal dose of the inotropic support (dopamine, 2 to 3 μg/kg/min). A two-dimensional echocardiogram revealed normal wall motion of the donor heart, demonstrating a mean (± SD) functional shortening of 0.23 ± 0.04 before transplantation and 0.21 ± 0.03 after transplantation (p = not significant [NS]). Oxygenation was demonstrated by blood gases with a mean (± SD) Po2 of 89.6 ± 2.9 mm Hg on room air before transplantation and 87.8 ± 3.4 mm Hg after transplantation (p = NS). The sternotomy was closed without loss of cardiac function, demonstrating a mean (± SD) arterial pressure of 98 ± 11 mm Hg before closure and 93 ± 15 mm Hg after sternal repair; and a mean (± SD) left atrial pressure of 12 ± 4 mm Hg before sternal closure and 14 ± 3 mm Hg after sternal repair (both p = NS).

Twelve animals awoke enough for the spontaneous ventilation to separate from the ventilator within 6 h after transplantation. Three animals remained anesthetized but awoke and obtained the spontaneous breath 10 h after transplantation.

Comments

The first experiments in heart and heart and lung orthotopic transplantations were performed in dogs.
by Demikhov in the 1940s. However, experimental studies regarding canine heart and lung transplantation have been limited because most experimental studies of easily orthotopic graft rejection are complicated by an inability to separate rejection-specific inflammatory mediators from nonspecific cardiopulmonary bypass effects, and cardiopulmonary bypass-related disturbances appear to lead to respiratory failure.

Experimental studies of orthotopic transplantation without cardiopulmonary bypass-related complications have been required despite the increased costs of and difficulties in maintaining these animals. Therefore, as Schäfers et al described, an experimentally reproducible canine model in orthotopic heart and lung transplantation without cardiopulmonary bypass has been desirable.

Additionally, the procedure of heart and lung transplantation gained renewed interest in the late 1980s when cyclosporine was induced in clinical and animal experiments conducted at Stanford University Medical Center. Essentially, the current method of human heart and lung transplantation involves the orthotopic en bloc transplantation of the trachea, pulmonary artery, left atrium, pulmonary veins, and aorta. Similar experimental models of heart and lung transplantation with a cost-effective procedure were also needed to evaluate the hemodynamic or immunologic condition of the transplanted organs for further studies of transplantation.

Recently, several canine models of heart and lung transplantation have been proposed, but survival was limited either because of respiratory failure or because of increased operative mortality associated with cardiopulmonary bypass. Among these studies, Kawaguchi et al proposed a new orthotopic heart and unilateral lung transplantation model using cardiopulmonary bypass. As they described, their model may be suitable for further studies of immunologic problems in cardiopulmonary transplantation, but this procedure needs cardiopulmonary bypass, and the recipient lung was preserved to avoid respiratory failure. Ertel et al presented similar models, but these models were achieved heterotopically with the heart and right lung of the recipient preserved. In order to obviate the need for cardiopulmonary bypass and preserve normal respiratory function, Schäfers et al presented an encouraging canine model without cardiopulmonary bypass during the operation. The donor heart and left lung were transplanted heterotopically with the preservation of the recipient heart and right lung. Actually, Schäfers et al have offered the advantages of preserving the normal respiratory gas exchanging function, which avoids the need of cardiopulmonary bypass, and the survival achieved in their study compares favorably with other surgical models. However, their model was achieved heterotopically with an en bloc heart and left donor lung transplantation. Therefore, their surgical procedure does not necessarily substitute a working cardiopulmonary unit that allows hemodynamic and respiratory studies after orthotopic cardiopulmonary transplantation.

The techniques we present in this article offer several advantages of completely replacing the total heart and bilateral lungs with donor organs and obviating the need for cardiopulmonary bypass. The essential step of this procedure requires a heterotopic implant of a ventilated heart and lung block, using partial occlusion clamps on target vessels. Once the second organs are in place, circulation and ventilation can be transferred gradually from the recipient to the donor, and then the native recipient organs can be resected, thereby leaving only the donor organ block to support the systemic circulation. The approach is greatly facilitated by placing a shunt between the recipient vena cavae, which greatly reduces technical barriers and reduces both ischemic and anastomotic time to < 1 h. The cardiac performance of the transplanted heart, such as cardiac output and left ventricular wall motion and oxygenation of the transplanted lungs, are preserved, at least acutely.

The surgical transplantation model in this article has several advantages. The procedure in our laboratory can do the following: (1) create a cardiopulmonary unit for hemodynamic, respiratory and immunologic studies in the orthotopic position of the donor organs; (2) be performed cost-effectively without cardiopulmonary bypass; (3) separate rejection-specific inflammatory mediators relating to cardiopulmonary bypass; and (4) acutely obtain stable hemodynamic and respiratory function of the transplanted organs and expect long-term survival. This report demonstrates the technical feasibility of orthotopic heart and lung transplantation without cardiopulmonary bypass using an acute animal model. Ongoing trials for achieving the chronic model are being conducted to evaluate the long-term hemodynamics and chronic heart and lung rejection of the transplanted organs.

References