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A Functional New Experimental Biventricular Model of Heterotopic Cardiac Transplantation

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ABSTRACT

A heterotopic cardiac transplantation model in which the donor heart was able to maintain the systemic and pulmonary circulation of the recipient was devised, which did not require extracorporeal circulation or heparinization. All donor hearts in five pairs of adult mongrel dogs were resuscitated, and the systemic and pulmonary circulations maintained by the donor hearts alone were studied hemodynamically up to 3 hr after resuscitation, although long-term survival was not achieved.

Key words: *Heterotopic cardiac transplantation, Working biventricular model, Mongrel dog*

A method of heterotopic cardiac transplantation in which anastomosis is made without using extracorporeal circulation has the advantages of both technical simplicity and low experimental cost. We have improved the working double heart model described by Ide et al[2] by simplifying the inferior vena cava anastomosis. This was a modified left ventricular bypass model, but the pulmonary circulation was maintained by both the donor and recipient hearts, since the only ascending aorta of the recipient was ligated. Therefore, we designed a more complete heterotopic cardiac transplantation model in which the systemic and pulmonary circulation could be maintained by the donor heart alone, like orthotopic cardiac transplants. Operative procedures and hemodynamic studies of this new model using mongrel dogs are described in this paper.

MATERIALS AND METHODS

Five pairs of adult mogrel dogs underwent cardiac transplantation by a newly designed method of heterotopic cardiac transplantation (Fig. 1). Under the anesthesia by ketamine injection (10 mg/kg, i.m.), the donor dog was intubated, connected to a respirator and prepared for removal of the donor heart through a left 5th intercostal thoracotomy. For cardiopegia, 20 ml/kg of Bretschneider's solution was infused into the left innominate artery through a retrograde insertion catheter. After rapid cardiac arrest, the donor heart was removed and preserved in iced physiological saline. The recipient dog was anesthetized in the same way, connected to a restirator (Bird Mark III), and subjected to thoracotomy through the left 5th intercostal space, followed by incision of the pericardium. At first, a Dacron prosthesis (12 mm in diameter) treated by preclotting was sutured to the right atrium, and the donor heart was anastomosed to the recipient heart by continuous suture in the order of the left atrium, pulmonary artery and aorta, anastomosing the descending aorta of the donor heart to the recipient heart's aorta. The anastomoses were performed by clamping the vessels partially. During the operation, no heparin was used.

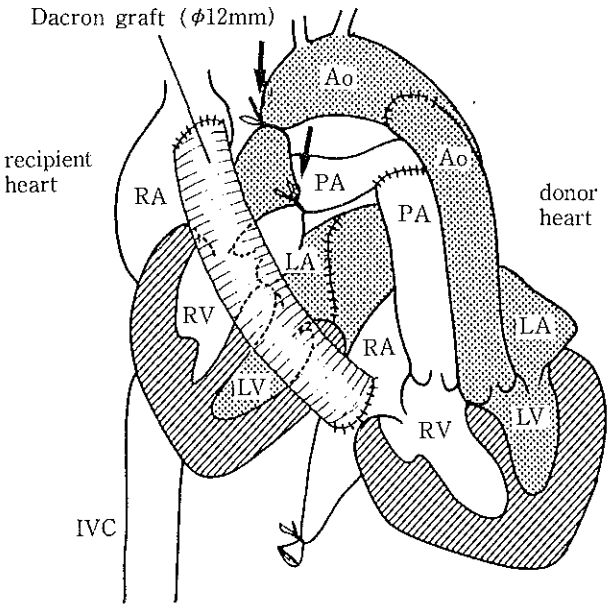

Fig. 1. New model of heterotopic cardiac transplantation. (Working biventricular model)
Pulmonary and systemic circulation was maintained by only the donor heart after ligation of both great vessels. (↓)

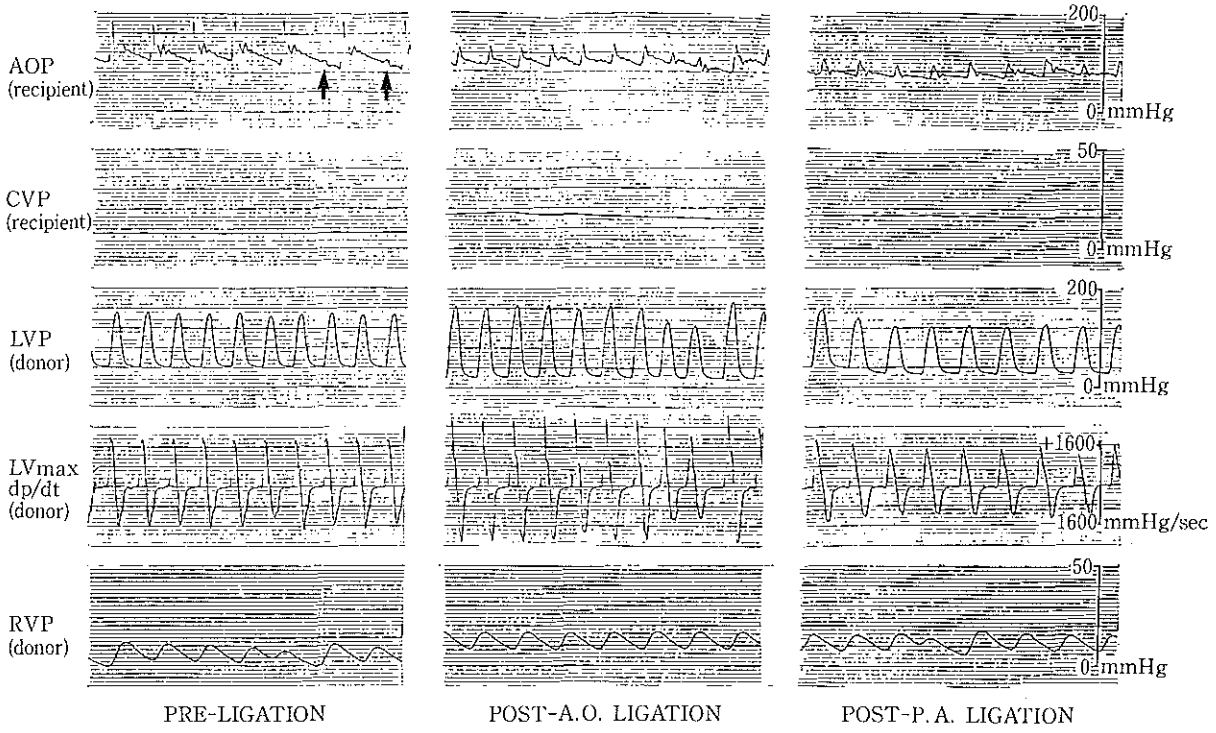

Fig. 2. Typical Hemodynamic changes associated with heterotopic cardiac transplantation.
AOP consisted of biphasic arterial pressure in the donor heart (⬆) and the recipient heart before aortic ligation. LVP and RVP of the donor heart increased after aortic ligation, but decreased gradually after P.A. ligation.

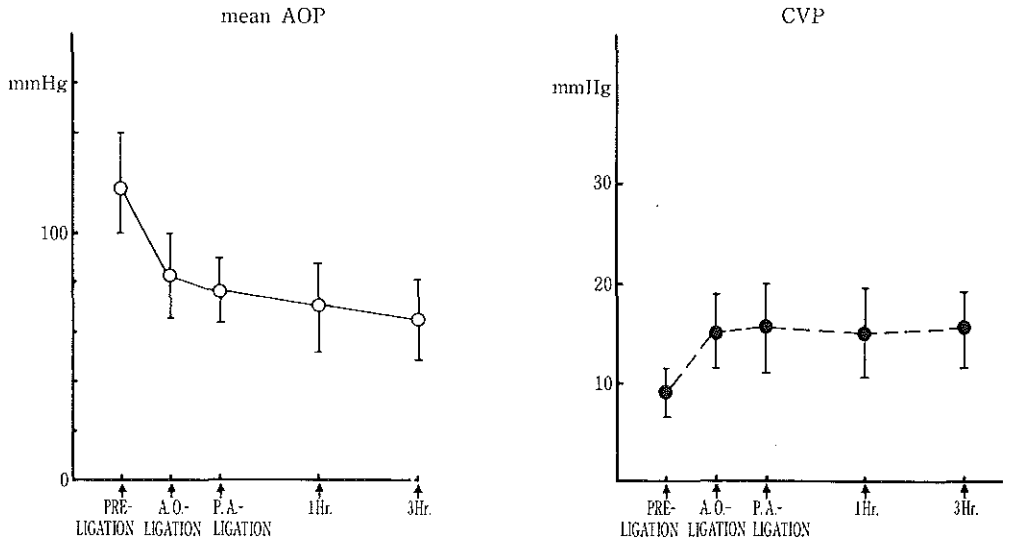

Fig. 3. Time course of changes in AOP and CVP after cardiac transplantation in 5 pairs of dogs.
AOP was reduced after the ligation of both great vessels and declined for 1 hr but maintained a constant level thereafter. CVP increased after the ligation of both great vessels.

Finally, the other end of Dacron prosthesis which has been previously sutured to the right auricle of the recipient heart was anastomosed to the auricle of the donor heart. The cardiac pulsations of the donor heart was restored by releasing each vascular clamp, and when the cardiac pulsations of the donor heart became powerful, both ascending aorta and pulmonary trunk of the recipient were ligated by a ligature which had been positioned previously. Thereafter, systemic and pulmonary circulation were maintained by the donor heart alone (Fig. 1).

Hemodynamic variables such as arterial pressure (AOP), central venous pressure (CVP), left ventricular pressure (LVP), right ventricular pressure (RVP) and the LV maxdp/dt of the donor heart were measured before and 1 and 3 hr after the ligation of the great vessels.

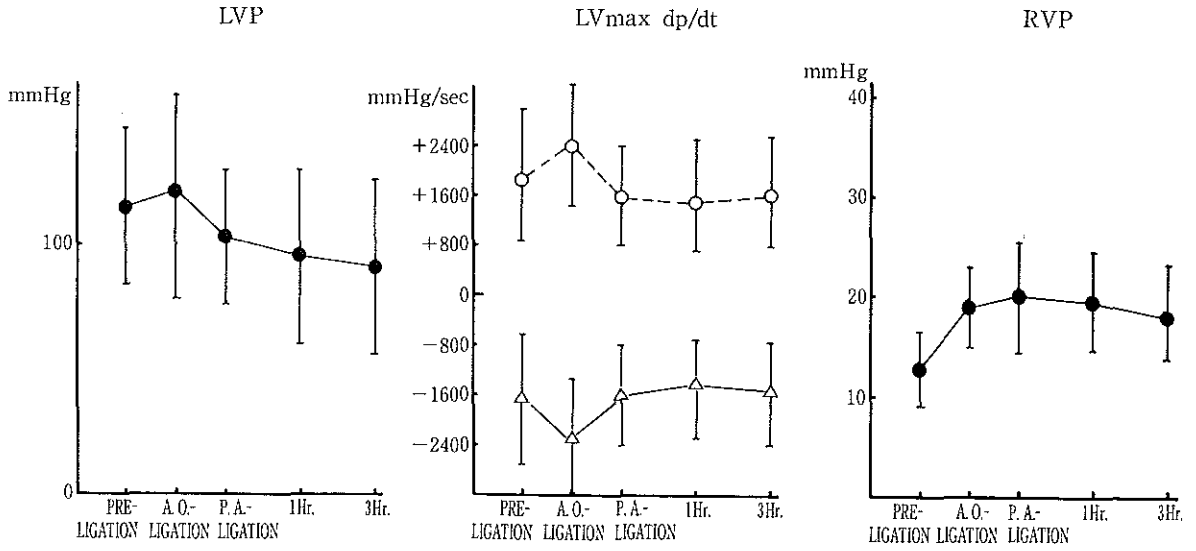

Fig. 4. Hemodynamic changes in the donor heart after heterotopic cardiac transplantation.
LVP and LV maxdp/dt increased slightly after aortic ligation, but afterwards decreased the over time. RVP increased stepwise following ligation of each great vessels.

RESULT

All five donor hearts resumed cardiac pulsation after completion of the anastomosis to the recipient heart. The mean of preservation time in iced saline and the time of the anastomosis of the recipient heart to the donor heart were 128 min and 56 min, respectively. Accordingly, the mean time of ischemia of the hearts was 184 min. Fig. 2 shows the changes in the AOP, CVP, LVP, RVP and LV maxdp/dt of the donor heart, before and after the ligation of the great vessels. Before ligation of the aorta, the AOP was biphasic and AOP of the recipient heart was much higher than that of the donor heart, and after ligation of the ascending aorta of the recipient heart, the CVP, RVP, and LV maxdp/dt of the donor heart all rose. After ligation of the pulmonary artery, although the CVP and RVP were almost unchanged, the AOP, LVP and LV maxdp/dt decreased slightly. The results indicated a stenosis of the pulmonary artery, because of a big difference in the size of the anastomosis between the pulmonary artery and the Dacron prosthesis sutured to the right atrium.

Fig. 3 shows the time course of changes in the AOP and CVP after cardiac transplantation in 5 pairs dogs. The AOP was reduced after ligation of both great vessels, but it stabilized 1 hr later, and thereafter the AOP was maintained at a relatively constant level. On the other hand, the CVP rose significantly after ligation of the aorta. Ligation of the pulmonary artery increased the CVP slightly, but thereafter it remained nearly constant.

Although the LVP of the donor heart increased with the increase of the blood flow into the donor heart after the ligation of the aorta, the LVP was decreased by the ligation of the pulmonary artery and thereafter decreased gradually. The LV maxdp/dt showed almost the same changes over time. The RVP increased stepwise after ligation of the aorta and pulmonary artery, but gradually decreased thereafter (Fig. 4).

However, long time survival could not be achieved. After ligation of both great vessels, the donor heart maintained the systemic and pulmonary circulation for 4—16 hours. The longest survivor lived vigorously for 16 hours but the donor heart stopped gradually after closing the chest wall, presumably because of compression to the donor heart and inflation deficiency of the left lung.

DISCUSSION

Heterotopic cardiac transplantation was reported first by Mann et al[4] in 1933. They developed a cervical heterotopic cardiac transplant model as nonfunctioning heart in which the heart of a small dog was transplanted into the neck of an adult mongrel dog. Since then, various simplified models of extrathoracic cardiac transplantation have been developed[5,9]. In 1966, McGough[7] developed a method of cardiac transplantation in which the donor heart was anastomosed to the recipient heart in the left thorax and had the right and left ventricle anastomosed to each other by partial bypass. Barnard et al[1] successfully performed the first clinical heterotopic cardiac transplantation under extracorporeal bypass.

Since the primary objective of cardiac transplantation is to remove a poorly functioning native heart and replace it by a healthy donor heart anatomically, orthotopic cardiac transplantation is most rational. In the experimental cardiac transplantation, however, orthotopic cardiac transplantation requires extracorporeal circulation and use of heparin, which are very invasive to the recipient, and make

long-term survival after transplantation more difficult. In addition, high costs make repeated experiments difficult.

Accordingly, to evaluate the function of the donor heart, experimental animal models of intrathoracic heterotopic cardiac transplantation requiring neither extracorporeal circulation nor heparinization, have been devised by Jamieson[3], Schaff[8] and Matsumoto et al[6]. Recently Ide[2] reported a technique of heterotopic cardiac transplantation in which the RV of the donor heart is bypassed partially, and the pulmonary and systemic circulation are maintained independently. All previous methods consisted of LV partial bypass, whereas, in Ide's model, systemic circulation is maintained by the LV system of the donor heart alone as a complete LV bypass. Therefore, Ide's model is believed to be an advance in heterotopic cardiac transplantation. However, pulmonary circulation in his model was maintained by partial RV bypass with contributions from both the donor and recipient hearts. In this sense, Ide's model is not a complete biventricular bypass model maintaining the systemic and pulmonary circulation by the donor heart alone. In the ideal experimental model, the donor heart could maintain both the systemic and pulmonary circulation by itself, like orthotopic cardiac transplantation. In this experiment, the right atrium and left atrium, pulmonary artery and aorta of the donor heart each was anastomosed to its corresponding part in the recipient heart, and then pulmonary trunk and aortic root of the recipient were ligated. Although the donor heart was functional during the acute phase after transplantation and hemodynamic evaluation of the donor heart was able in RV and LV independently, long-term survival was not achieved. Therefore, operative technique and postoperative care remain problems to be improved in the future. In addition, this model is unsuitable for the clinical application, because, circulatory assistance to the donor heart by the recipient heart, which is one of the advantage of biventricular bypass form in heterotopic cardiac transplantation, is lost in this model.

Improvable problems of this model are: 1) Improvement of the anastomoses between the RAs and LAs to obtain adquate preload for the RV and LV, especially, the connection between the venous systems without using an arterial prosthesis, as was used between the RAs in the present experiment. 2) Trial use of an artificial chest wall to expand the left chest wall to reduce compression of the left lung by the donor heart after closing chest, and 3) Improved myocardial protection during implantation of the donor heart. Considering these problems, further experiments will be required to achieve long-term survival.

CONCLUSION

1. A heterotopic cardiac transplantation model which systemic and pulmonary circulation can be maintained by the donor heart alone was devised by the anastomosis of the heart in the dog without using extracorporeal circulation and heparin.
2. The heterotopic cardiac transplantation was performed using five pairs of mongrel dogs. Pulsation of the donor heart resumed in all transplants, and the function of both ventricle was evaluated.
3. For obtaining a long-term survival, following consideration will be required: 1) postoperative active management for the inflation deficiency of the left lung, 2) improvement of the atrial anastomosis for obtaining sufficient pre-load, and 3) strict myocardial protection during anastomosis of the donor heart.

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