Novel technique for isolated accessory right heart transplantation for congenital heart disease

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Background: Our prior laboratory work has permitted adding a whole donor heart to a preserved recipient right heart, producing a heart-and-a-half preparation able to cope with pulmonary hypertension in the recipient. The experiments in the present study explore the feasibility of the converse operation: adding an isolated donor right heart to an entire preserved heart.

Methods: Eight adult mongrel dogs (4 donors and 4 recipients) were used in 4 transplant operations performed through a right thoracotomy without cardiopulmonary bypass (using side-biting control of recipient vessels). The donor heart underwent resection of the left atrium and left ventricle, leaving an isolated donor right heart. Blood supply to the donor right ventricle was preserved from the donor ascending aorta. Through a right thoracotomy, the donor right heart was transplanted in parallel to the native right heart of the recipient by using the following anastomoses: (1) donor superior vena cava to recipient superior vena cava (end-to-side anastomosis); (2) donor pulmonary artery to recipient pulmonary artery (end-to-side anastomosis); (3) donor ascending aorta to recipient aorta (through a great vessel [end-to-end anastomosis] to provide arterial inflow to donor coronary arteries). Animals were euthanized within 1 hour after completion of transplantation.

Results: Isolation of the right ventricle by excision of the left chambers was technically feasible. Transplantation without cardiopulmonary bypass was feasible in all cases. The isolated right heart beat well after transplantation in all animals, demonstrating sinus rhythm. Three of 4 animals were able to sustain good hemodynamics on support with epinephrine. Bleeding from the septum or aortic valve of the donor (now open to the pericardial space) was not problematic. Mean arterial pressure was 85 mm Hg (mean) at a right atrial pressure of 6 mm Hg (mean). In 2 animals the recipient superior vena cava was ligated to obligate upper body flow to pass through the accessory ventricle; hemodynamics were preserved under these circumstances.

Conclusion: Transplantation of an isolated right heart is feasible. Such a technique has potential as a novel therapeutic alternative for obstructive or hypoplastic lesions of the right heart in human children.

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Received for publication June 28, 2002; revisions requested Aug 20, 2002; revisions received Sept 5, 2002; accepted for publication Sept 17, 2002.

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J Thorac Cardiovasc Surg 2003;125:1283-90

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0022-5223/2003 \$30.00 + 0

doi:10.1016/S0022-5223(02)73617-9

Prior work in our laboratories has demonstrated the feasibility of preserving the recipient right heart while transplanting an entire donor heart, resulting in a one-and-a-half-heart preparation.¹ That work was motivated by the goal of preserving the native right heart as a natural assist for the donor right heart in combating pulmonary hypertension in recipients. The effectiveness of this model against iatrogenic pulmonary hypertension has recently been demonstrated in our laboratories.²

Figure 1. Schematic view of the isolated right heart remaining after excision of the LV. Note preservation of the LAD. The PDA is also preserved (not shown). Note ligation of the coronary sinus. Also shown are the long stumps preserved to facilitate later anastomoses: right PA, innominate and right subclavian veins, and entire aortic arch. Note the hemostatic over-and-over suture on the free edge of the former LV. Note that the aortic valve is exposed on its inflow side to the pericardial space.

Having thus achieved the separation of the right and left sides of the heart, we decided to explore the converse operation: adding a donor right heart to a preserved complete recipient heart. This technique, if feasible, could provide a novel alternative treatment for congenital hypoplastic lesions of the right heart.

The experimental work presented here explores the feasibility of this converse operation: transplantation of an isolated right heart to supplement a preserved recipient heart.

Methods

After review by the Yale University Institutional Animal Care and Use Committee, surgical experiments were performed on 8 mongrel dogs weighing 35 to 40 kg. Four dogs served as donors, and 4 were recipients. Side-by-side operating tables allowed the donor and recipient operations to be carried out simultaneously. Arterial blood pressure, pulmonary artery (PA) pressure, body temperature,

oxygen saturation, arterial blood gases, and electrocardiographic results were monitored and recorded. The PA catheter was withdrawn during transplantation to permit clamping of and anastomosis to the PA.

Donor Procedure

The donor operations were carried out according to established clinical procedures used at our center for human transplantation. The inferior vena cava (SVC) is incised initially to prevent right heart dilatation during cardioplegia administration. Donor heart preservation is done by instilling cardioplegic solution into the aortic root (our institutional standard crystalloid cardioplegic solution, containing 20 mEq KCl/L at 4°C) and topical hypothermia. The venae cavae are transected. The aortic arch and PA are transected. The pulmonary veins are then transected to complete the explantation. The entire SVC, as well as the proximal portion of the right subclavian vein (after ligation of the azygos vein), is harvested to expedite the later right heart anastomosis. The as-

Figure 2. PA anastomosis done in the fissure between lobes and performed in an end-to-side fashion.

cending aorta and aortic arch are harvested (after the great vessels are divided) to facilitate the later aortic anastomosis. The left PA of the donor is preserved maximally to optimize anatomic reach for the later anastomosis.

Recipient Procedure

The recipient is cannulated through the right femoral artery and vein for monitoring of the systemic arterial pressure and the PA pressure. The right side of the chest is entered through a thoracotomy incision in the fourth intercostal space. The SVC is then isolated, and vessel loops are placed for control. The right PA is isolated likewise beyond the right middle lobe branch and within the horizontal fissure.

Excision of the Donor Left Ventricle

Excision of the donor left ventricle (LV) is illustrated in Figure 1. The donor's LV is excised 1 cm beyond the interventricular groove along the anterior wall just to the left of the left anterior descending coronary artery (LAD). Diagonal arteries are ligated according to their size. The resultant incision is extended caudally around the left ventricular apex to the inferior wall. Of note, the posterior descending coronary artery is preserved, as well as the LAD. The main trunk of the posterolateral branch of the right coronary artery

is divided as it runs laterally to the posterior surface of the LV in the atrioventricular groove. The coronary sinus is also ligated. The excision of the LV is then carried anteriorly across the left ventricular outflow tract underneath the aortic valve. The left ventricular excision is completed by incising the lateral wall of the LV just caudal to the atrioventricular groove and the mitral valve annulus. The circumflex artery is then ligated, along with the marginal branches. Finally, the LV is removed from the operative field once the chordal attachments are cut, thereby releasing the LV with the papillary muscles still attached. The remaining cut edge of the LV is then oversewn with a running over-and-over suture, achieving complete hemostasis. As described, this method preserves direct circulation to the right heart tissue through the acute marginal branches of the right coronary artery, the posterior descending artery and its septal perforating branches, and the LAD and its septal perforating branches. The free wall of the left atrium containing the pulmonary vein orifices is also excised. A patent foramen ovale, if found, is closed.

Right PA Anastomosis

Right PA anastomosis is illustrated in Figure 2. Heparin (70 U/kg) is administered intravenously before the first anastomosis. The donor left PA is anastomosed end to side to the recipient's right PA

Figure 3. SVC anastomosis performed in an end-to-side fashion. Note that the azygos vein of the donor has previously been ligated.

in a convenient location within the midportion of the horizontal fissure. The anastomosis is carried out with a running 7-0 suture after the proximal and distal control snares are tightened to allow a relatively bloodless field. This anastomosis provides outflow from the donor right heart.

SVC Anastomosis

SVC anastomosis is illustrated in Figure 3. The donor SVC is anastomosed to the recipient's SVC in an end-to-side fashion. A side-biting clamp is used for SVC control. This anastomosis is performed by using a 5-0 or 6-0 suture in a running fashion. This anastomosis provides inflow to the donor right heart.

Aortic Anastomosis

Aortic anastomosis is illustrated in Figure 4. The donor aortic arch is evaluated to determine which aortic branch (innominate, left carotid, or left subclavian) will provide the best fit for a coronary inflow anastomosis. This inflow anastomosis will provide only coronary artery blood supply for the donor right heart. Once this is decided, the other branches (remnants of the donor's great vessels) are closed with a running 5-0 suture. One of the recipient's great vessels, usually the left subclavian artery, is borrowed to provide inflow to the coronary arteries of the donor right heart. The recipient subclavian artery is clamped, divided, and brought down for an end-to-end anastomosis to the selected

recipient aortic arch branch. This anastomosis is performed in an end-to-end fashion. Once this anastomosis is completed, the clamp on the subclavian artery is removed, and the donor's coronary arteries are perfused.

Topical hypothermia is used during the anastomosis process for donor right heart preservation. The entire procedure is done without cardiopulmonary bypass, with the donor heart beating and providing circulation. A single dose of steroid medication (200 mg of methoprednisolone; Solu-Medrol, Upjohn, Kalamazoo, Mich) is given to prevent acute rejection. No other immunosuppressive agents are used. The pulmonary anastomosis is released before the SVC anastomosis to prevent distention of the donor right heart. An epinephrine drip is started at $0.02 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and titrated to effect to stimulate the accessory right ventricle (RV) after the ischemic interval (during preparation and implantation), as is our practice in clinical transplantation.

At this point, the accessory right heart lies in the right side of the chest (Figure 5) suspended by its vascular anastomoses. The accessory right heart has, through these anastomoses, been connected in parallel to the native right heart. This is shown schematically in Figures 5 and 6.

The animals were observed for 30 to 60 minutes, hemodynamic measurements were taken, and the animals then euthanized. All composite recipient-donor heart preparations were excised and subjected to gross postmortem examination.

Results

In all 4 animals receiving transplants, the accessory right heart functioned well. The transplant procedure was able to be successfully accomplished through a right-sided thoracotomy without cardiopulmonary bypass. The operation proved technically feasible in all respects:

1. *Excision of the LV.* The donor LV was able to be excised alone without any ill effects.
2. *Prevention of bleeding.* Septal wall bleeding, if any, was minimal.
3. *Preservation of coronary blood supply.* Preservation of coronary blood flow to the accessory RV was successfully achieved, with a normal-appearing contraction pattern of the accessory RV.
4. *Technical feasibility of anastomoses.* All anastomoses were constructed successfully and hemostatically. Satisfactory reach and lie of all blood vessels was achieved. With care to harvest generous portions of all donor blood vessels, all anastomoses were well within reach of their anatomic counterparts. No interposition grafts proved necessary.
5. *Thoracotomy approach.* All anastomoses were able to be accomplished outside of the pericardial sac.
6. *Aortic valve competence.* The donor aortic valve was hemostatic. With this operation, the aortic valve becomes exposed to the pericardial space (after excision of the LV). The aortic valve proved entirely hemostatic. In some prior related animal experiments, we closed the aortic valve surgically by suturing to simulate the clinical scenario. In patients the aortic valve could not be relied on to prevent intrapericardial bleeding without being surgically closed.

None of the recipients were started on cardiopulmonary bypass. As in clinical transplantation, ventricular fibrillation of the donor heart occurred early in the rewarming process and responded to lidocaine administration, defibrillation, and intermittent ventricular pacing. All animals required epinephrine for initial hemodynamic support. The systolic arterial pressures ranged from 70 to 160 mm Hg, with a mean arterial pressure of 85 mm Hg. All of the animals sustained adequate hemodynamics with the accessory right heart online. In all animals the donor heart beat vigorously, although not in synchrony with the native heart. In one animal refractory fibrillation of the native right heart occurred several minutes after successfully initiating function of the accessory right heart. The accessory right heart was functioning well at that time.

Before the end point of the experiments, in 2 recipients the native SVC was occluded (by a clamp proximal to the end-to-side anastomosis of the donor heart), so as to oblige upper body venous return to pass through the donor right heart. Despite this occlusion, we observed preservation of systemic blood pressure between 85 and 100 mm Hg.

Figure 4. Arterial inflow anastomosis. The anastomosis is shown here constructed between the left subclavian artery of the donor (borrowed for use) and the left carotid branch of the donor aortic arch. This anastomosis is performed in an end-to-side fashion. The sole purpose is to provide inflow to the coronary arteries of the donor right heart; any combination of aortic arch branches can be used.

There was no obvious evidence of donor right ventricular strain under these circumstances.

Discussion

These experiments have shown that in the animal model isolated transplantation of an auxiliary right heart is feasible. Hemostasis, coronary perfusion, and maintenance of sinus rhythm proved feasible.

Patients who have a hypoplastic right heart or univentricular heart have been palliated for many years with the Glenn shunt or variations of the Fontan procedure, in which the right heart is bypassed and the lungs are perfused by venous pressure.³ Flow is surgically established from the SVC, inferior vena cava, or right atrium directly into the PAs. Although satisfactory palliation is often achieved for years, many of these patients experience clinical deterioration over several decades because of arrhythmias, increasing pulmonary vascular resistance (PVR), and ventricular failure.⁴ The experimental procedure described in this report

Figure 5. The completed operation. Note that the accessory right heart hugs the right border of the native heart but lies in the right pleural space.

could have clinical application for such patients. The accessory right ventricular heart transplantation described in this report permits ventricle-powered extra-anatomic lung perfusion.

Isolated right heart transplantation has several potential advantages for this population compared with standard heart transplantation. Many of these patients have a well-functioning systemic ventricle, so that only the addition of a pulmonary ventricle is truly required. The technique developed in the present series of experiments preserves the well-functioning native systemic ventricle. Unlike conventional heart transplantation, the systemic circulation is not rendered subject to potential rejection of the systemic ventricle. Rejection of an isolated accessory right heart would be expected to have lesser clinical effect, allowing for a larger margin of safety. Even in the case of rejection, the accessory right heart should provide a passive conduit be-

tween the venous and pulmonary circulations. This novel procedure is not intended for situations in which there is accompanying recipient left heart dysfunction or severe pulmonary hypertension, in which case standard orthotopic or heterotopic transplantation might be necessary.

In terms of potential future candidate selection, the recipient population for this procedure would not have prohibitively high PVR, having already been palliated with the Fontan circuit. A normally functioning accessory right heart should be able to maintain good function in a setting of normal or only moderately increased PVR. In addition, the donor population for the procedure could be much larger than the traditional donor pool. Many donor hearts with decreased LV function might have well-functioning RVs and thus would be donor candidates, even though their LVs would be unsuitable for use in conventional heart transplantation. Removal of the donor LV results in a transplanted

Figure 6. Schematic diagrams of resultant circulation. Note that the accessory right heart is connected in parallel with the native right heart.

organ with much smaller mass, facilitating implantation in the right side of the chest without causing interference with other vital thoracic organs.

Our previous studies have shown the feasibility of separating the left and right sides of the heart.^{1,2} The present investigation demonstrates a method for transplanting the isolated right heart with good immediate function. Multiple potential technical problems, including achievement of adequate blood supply to the isolated right heart and technical feasibility of anastomoses, have been successfully overcome in this series of experiments.

This was specifically a feasibility study. The animals were euthanized approximately 1 hour after stable hemodynamics were confirmed. These experiments were performed on normal recipient animals without chronic congenital heart disease. Further studies are needed to detail the physiologic relationship of the 2 RVs, including PA pressures, blood flow in each of the 2 parallel right heart circuits, and accessory right ventricular valvular function. Longer-term survival experiments are appropriate to determine long-term function with 2 parallel right hearts. Optimal synchronization of the 2 right hearts will need to be explored, as has been done with heterotopic transplantation. However, even without further refinement, in the operation reported in this article, each ventricle is beating synchronously with its own atrium.

This procedure is not intended to replace current surgical therapy for infants and children with univentricular hearts because current management is satisfactory without the risks associated with immunosuppression and rejection. Rather, we envision this procedure to have application to older individuals with clinical deterioration late after initial palliation with Glenn or Fontan procedures. Although conventional reoperation on patients whose condition is deteriorating late after traditional univentricular heart procedures produces some palliation,⁵ one could expect many advantages from establishing a 2-ventricle system. These advantages could be reflected in increased exercise capacity, avoidance of arrhythmias, and prolongation of life expectancy. A fully functioning right heart will likely decrease central venous pressure, ameliorating right heart failure associated with the passive Fontan flow and avoiding atrial distention and its associated arrhythmias. The transplanted right heart can be expected to accommodate over time to overcome any modest increase in PVR, unlike the Fontan circuit, in which a small increase in PVR can lead to significant decompensation.

We believe that the novel accessory right heart transplantation technique reported here might have application as an alternate therapy to traditional heart transplantation for the group of patients with longstanding univentricular physiology with progressive circulatory dysfunction.

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