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Neonatal model of heterotopic heart transplantation in pigs

To investigate the long-term success of heart transplantation in newborn infants who have complex congenital heart disease, we have developed a model of heterotopic heart transplantation in immature pigs. We chose the heterotopic technique because it is simple, does not require cardiopulmonary bypass or heparin, allows for significant size disparity between the recipient and donor hearts, and allows for experimental comparisons between the two hearts. Small newborn piglet hearts are harvested, prepared, and then transplanted into the left chest of larger weanling pigs to augment or substitute for the native left ventricle. Preliminary data from transplants into 49 pigs suggest that the technique is technically possible, the pigs can be immunosuppressed over the long term, and the donor heart can contribute hemodynamically. Experimentally, the model is well designed for the investigation of issues critical for the long-term success of heart transplantation in infants and children, including growth and development, optimal long-term immunosuppression, differences in immunotolerance, and the study of coronary obliterative disease. Clinically, the model has potential applicability in congenital heart anomalies if one native functioning atrium and ventricle are present.

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Orthotopic cardiac transplantation has become a widely accepted therapeutic option for the treatment of acquired end-stage heart disease in adults.[1] Although this modality has been applied recently to infants and children, it is limited by the requirement of a close size match, the need for immediate function, the lack of interim external support measures, the need for mature donor tissues, and the need for systemic heparinization and cardiopulmonary bypass.[2]

Heterotopic transplantation offers a number of potential advantages over the orthotopic approach[3-5]: (1) The technique is simpler, (2) there is no need for systemic heparinization or cardiopulmonary bypass, (3) organ size disparity between donor and recipient is better tolerated, (4) the technique can be used in patients earlier in their disease course, (5) the recipient heart is preserved to allow for its own potential recovery and to improve overall hemodynamic function during the early posttransplant recovery phase, (6) the transplant can be removed if complications ensue, (7) the technique can be used selectively in some patients with pulmonary hypertension, and (8) circulatory hemodynamics may be better maintained during episodes of acute rejection. This technique holds particular promise for patients with congenital heart disease, since most complex congenital heart anomalies have one functioning atrial collecting chamber and one functioning ventricular pumping chamber. A heterotopic heart transplant could then act as a biologic assist device[6-8] or as a substitute for the absent, vestigial, or compromised ventricular pumping chamber.

Although many models of heterotopic cardiac transplantation have been described in large animals,[4,5,9] no immature donors or recipients have been used. In this study, we report the development of a neonatal model of

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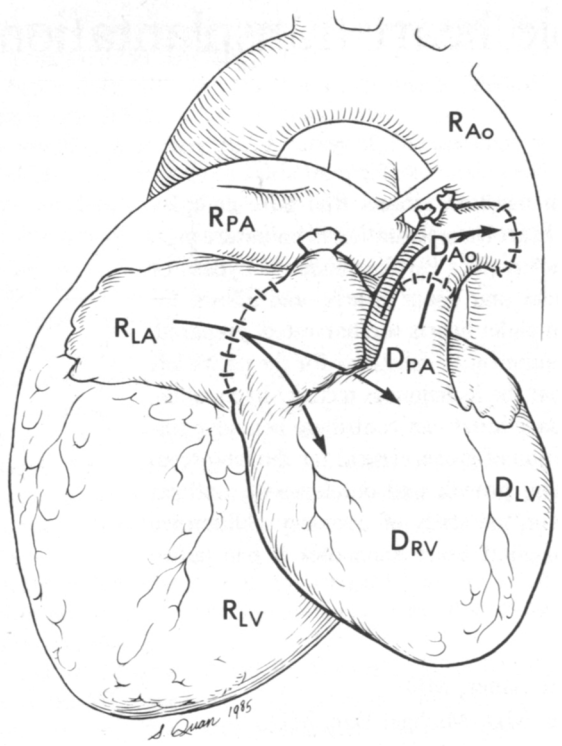

Fig. 1. Diagram of the neonatal heterotopic heart transplantation model. *R*, Recipient; *D*, donor; *Ao*, aorta; *PA*, pulmonary artery; *LA*, left atrium; *LV*, left ventricle.

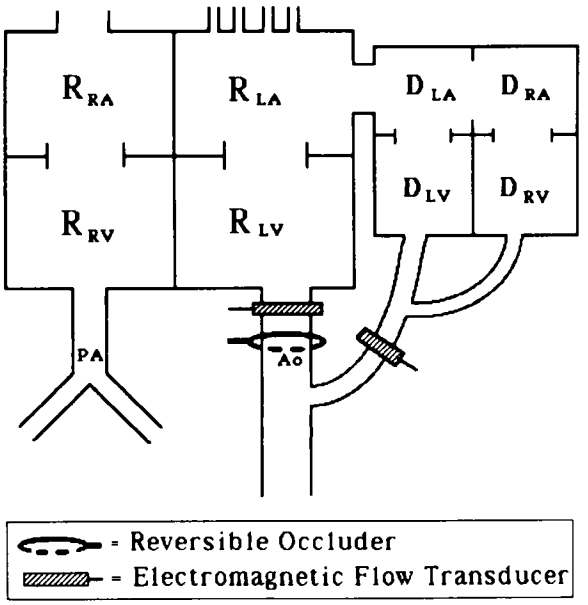

Fig. 2. Schematic representation of the neonatal heterotopic heart transplantation model. For abbreviations see Fig. 1.

heterotopic heart transplantation in immature pigs and describe preliminary technical feasibility, immunosuppression, and hemodynamic results. We chose to bypass the left side of the heart because of the poor clinical results in hypoplastic left heart syndrome with current palliative techniques.[10] This model is suitable for the investigation of several important issues in neonatal heart transplantation, including (1) individual growth and development of the recipient and the transplant, (2) optimal long-term immunosuppression, (3) hemodynamic compensation by the transplant for the failing heart, (4) possible differences in immune tolerance of the immature heart, (5) techniques for noninvasive diagnostic surveillance of rejection, and (6) the study of coronary obliterative disease with the recipient heart as a control.

Materials and methods

Animals. Forty-nine pairs of York-Hampshire pigs were obtained form Pork Power (Tracy, Calif.). Donors were newborn pigs weighing 1 to 3 kg. Recipients were weanlings (aged 2 to 3 months) weighing 8 to 10 kg. All pigs received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals," prepared by the National Institutes of Health (NIH Publication No. 80-23, revised 1978).

Donor harvest and preparation. The donor was anesthetized with inhalational halothane (0.1%) and oxygen. A tracheostomy was performed, and the piglet was ventilated with a pediatric ventilator (Harvard Apparatus Co., Inc., S. Natick, Mass.). Carotid arterial and jugular venous catheters were placed for pressure monitoring and infusion of crystalloid solution, respectively. The adequacy of ventilation and oxygenation was assessed by arterial blood gas analysis.

Through a median sternotomy, the pericardium was opened and the superior and inferior venae cavae, ascending aorta, and pulmonary artery were isolated. In phase III, precalibrated electromagnetic flow transducers (4.0 to 6.0 mm Fr; Invivo Metrics, Healdsburg, Calif.) were placed on the ascending aorta and/or main pulmonary artery, and a catheter was placed through the apex of the left ventricle into the ventricular cavity to monitor left ventricular pressure.

The donor harvest was performed in the following manner. Heparin (3 mg/kg) was given intravenously. The superior vena cava was ligated, the aortic arch was crossclamped, and a cold (4° C), hyperosmolar (320 mOsm), high-potassium (18 mEq), crystalloid cardioplegic solution (20 ml/kg) was infused into the proximal ascending aorta. The heart and lungs were removed en bloc and placed in a cold topical saline solution for ex vivo preparation. A second dose of cold cardioplegic solution (10 ml/kg) was often given after 30 minutes to maintain myocardial preservation.

The heart was then separated from the lungs and the ductus arteriosus was ligated and divided. The main pulmonary artery was obliquely transected proximal to its bifurcation and

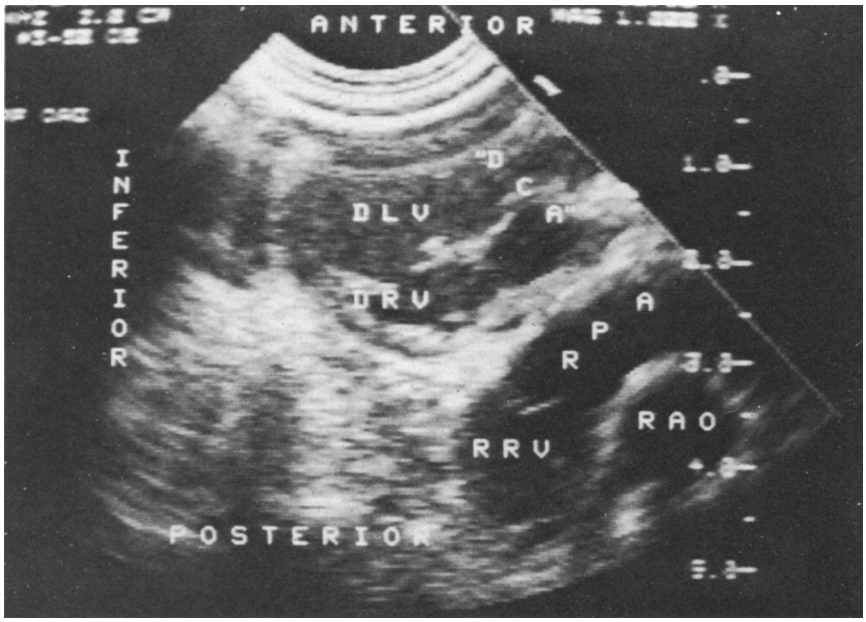

Fig. 3. Two-dimensional Doppler echocardiogram of neonatal heterotopic heart transplant. This view is obtained through the lateral left chest wall with the donor heart closest to the transducer. *DCA*, Donor coronary artery. For other abbreviations see Fig. 1.

anastomosed end to side to the ascending aorta. This procedure created a single biventricular outflow tract similar to a truncus arteriosus (Fig. 1). A left atriotomy was made at the confluence of the pulmonary veins, and a generous atrial septectomy was performed. Intercostal and bronchial arteries emerging from the aorta were ligated with fine sutures. The innominate artery, which had been previously cannulated from the carotid artery in the neck, and the left ventricular catheters were preserved to act as air vents during transplantation and for later hemodynamic monitoring.

Recipient preparation. Recipient weanling pigs were sedated with ketamine (10 mg/kg intramuscularly), anesthetized by face mask with the oxygen-halothane mixture, and then intubated orally. Arterial blood gases were carefully monitored. For phase III acute hemodynamic studies, polyvinyl catheters were placed in the right common carotid artery, the right atrium via the right internal jugular vein, the femoral artery, and the femoral vein. A left lateral thoracotomy was performed with resection of the fourth rib. In phase III, the pericardium was opened wide and the main pulmonary artery, ascending aorta, and descending aorta were dissected for flow transducer and constrictor placement. A left ventricular catheter was placed through the apex of the heart. For long-term studies, only a small (3 cm) incision was made in the pericardium to expose the left atrium.

Transplantation. Heterotopic transplantation was performed without heparin or cardiopulmonary bypass. The recipient left atrium was partially clamped in an oblique orientation with a Satinsky vascular clamp. The donor common atrium was then anastomosed to the recipient left atrium, side to side, with a running 6-0 polypropylene suture. The donor aorta was then anastomosed to the descending recipient aorta end to side (Fig. 1).

Before removal of the vascular clamps, the recipient was given sodium bicarbonate (2 mEq/L), and a dopamine infusion (5 mg/kg/min) was started. Maneuvers to remove air from the donor heart were extremely important. First, a small clamp was placed close to the donor aortic valve, and the distal donor aorta was filled from the recipient aorta by removing the crossclamps on the recipient descending aorta. The donor aorta was vented through the innominate artery catheter. The left atrial clamp was removed and the donor left ventricle was vented through the left ventricular catheter by tilting the heart upward and gently massaging out any air. Finally, the clamp at the root of the aorta was removed to perfuse the donor coronary arteries. The heart rewarmed rapidly and coarse ventricular fibrillation resulted, which occasionally converted to sinus rhythm spontaneously but usually necessitated cardioversion. The entire harvest, donor preparation, and transplantation usually took less than 60 minutes.

Protocol

Phase I: Feasibility studies. The 24 pigs used for phase I studies underwent transplantation without hemodynamic studies or long-term immunosuppression. Epicardial electrocardiograms were obtained immediately after the operation on both donor and recipient hearts and were repeated on postoperative day 2 and just before the pigs were killed. Histologic examination was performed on all donor hearts when the animals were put to death, which was up to 10 days postoperatively.

Phase II: Long-term immunosuppression. The 19 pigs used for phase II studies received 9 mg/kg/day of intravenous cyclosporine (Sandoz Pharmaceuticals, E. Hannover, N.J., and 4 mg/kg/day of intravenous methylprednisolone (Solu-Medrol) until they were eating well. Then they were switched to an oral dose of 0.25 ml/kg/day of cyclosporine and 2

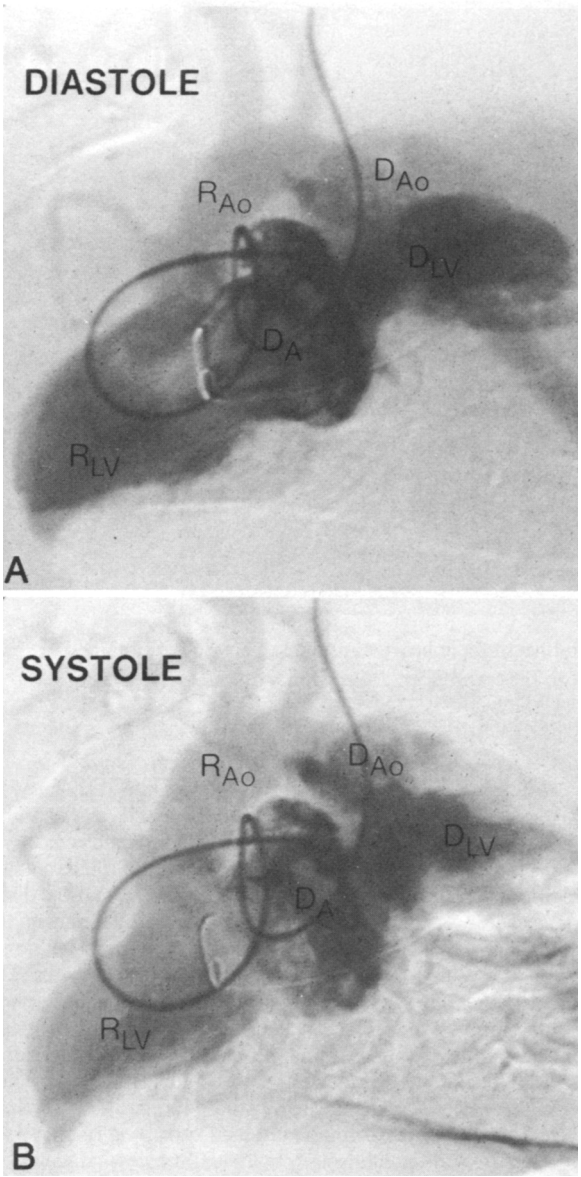

Fig. 4. Arteriographic images during diastole (**A**) and systole (**B**) of a neonatal heterotopic heart transplant. Contrast material was injected into the recipient left atrium through an indwelling catheter. *DA,* Donor atrium. For other abbreviations see Fig. 1.

mg/kg/day of prednisone. The prednisone was tapered to 0.6 mg/kg/day by the eighth postoperative day. Oral doses were given with some difficulty per os by syringe. In some later pigs, gavage feeding was accomplished by a small nasogastric tube, but these tubes were difficult to maintain over the long term. Electrocardiograms were routinely performed as in phase I.

The 17 surviving pigs underwent routine postoperative two-dimensional echocardiograms on postoperative days 4 to 6 to study contractile activity, direction of blood flow, and valvular competence. Echocardiograms were also performed for lethargy, poor feeding, or clinical suspicion of graft rejection. Two pigs underwent arteriography with the use of an indwelling left atrial catheter, and five pigs were given technetium 99m–labeled red blood cells for gated blood pool scans 2 to 8 days postoperatively. These nuclear scans were gated by using the epicardial electrocardiograms. The scans were oriented over the ventricular septum in both the donor and recipient hearts. Cardiac output and ejection fraction were then estimated for both hearts.

Table I. *Gated technetium 99m–labeled red blood pool scans*

	Cardiac output (ml/min)	*Ejection fraction (%)*
Recipients	2050 ± 645.5	44 ± 12.5
Donors	420 ± 125.8	30 ± 19.7

Values reported are mean ± standard deviation for five pigs.

Phase III: Cardiovascular hemodynamics. Five pigs underwent intensive hemodynamic monitoring of the pretransplant donor and recipient hearts and of the interaction between the hearts after transplantation (Fig. 2). Before transplantation, baseline pressures were measured in the recipient and donor left ventricle, right atrium, left atrium, and pulmonary arteries.

Stroke volume and cardiac output were measured from the electromagnetic flow transducer placed on the ascending aorta. A partial constrictor on the recipient aorta just distal to the flow transducer was then tightened to reduce cardiac output by 25% to 50%, and measurements were repeated.

After transplantation, the same pressures and flows were recorded under three conditions: (1) 100% recipient aortic blood flow; (2) approximate 50% reduction in recipient aortic flow by tightening the constrictor on the recipient aorta; and (3) ventricular fibrillation of the recipient heart resulting from ligation of the recipient left anterior descending coronary artery. In addition, stroke volume and cardiac output from the donor heart were estimated when the two hearts were beating synchronously or 180 degrees out of phase. All pressure and flow studies were done after the recipient's arterial pH, carbon dioxide tension, and oxygen tension had been normalized.

Results

Phase I. Eight of the 25 pigs survived, with both recipient and donor hearts contracting well. During this phase, we continually improved our anesthetic and surgical techniques to avoid identified causes of transplant failure: coronary air embolism; excessive use of cardioplegia; anesthetic-related deaths; excessively long aortic crossclamp time; or technical errors during the donor harvest, the donor preparation, or during the transplantation procedure itself. In the eight survivors, which were put to death between postoperative days 2 and 10, microscopic examination revealed various degrees of acute rejection indicated by lymphocytic infiltration and myonecrosis except in the pig killed early on day 2.

Phase II. Seventeen of the 19 pigs that received immunosuppressive drugs survived the operative proce-

Table II. *Hemodynamic pressures before and after heart transplant in immature pigs*

			Pressures (mm Hg)						
Time	*Animal*	*Condition*	*Right atrial*	*Left atrial*	*Left ventricular end-diastolic*	*Pulmonary artery mean*	*Left ventricular systolic mean*	*Carotid arterial systolic*	*Femoral arterial systolic*
Before transplant	Donor	Baseline	2.1 ± 1.2	2.4 ± 0.9	2.0 ± 1.2	9.4 ± 4.4	62.5 ± 8.7		
	Recipient	Baseline	4.8 ± 3.2	5.2 ± 1.0	7.2 ± 4.0	16.0 ± 5.1	71.4 ± 9.9		
		Constricted	4.4 ± 2.1	14 ± 8.5	15.3 ± 7.3	11.7 ± 2.1	101 ± 12.2		
After transplant	Donor	Baseline			3.7 ± 2.5		40 ± 16.9		43 ± 11
		Constricted			4.7 ± 1.2		36.7 ± 16.3		
		V. Fib.			7.3 ± 4.2		33 ± 5.3		
	Recipient	Baseline	6.1 ± 3.6		3.3 ± 1.2		99.0 ± 4.6	78 ± 14	
		Constricted	5.3 ± 4.2		4.0 ± 2		94.2 ± 14	67 ± 21	55 ± 20

Data are mean ± standard deviation for five pigs before transplantation and three pigs after transplantation. Constricted, Reduction of recipient aortic blood flow and pressure by 25% to 75% by constricting the ascending aorta; V. Fib., ventricular fibrillation of the recipient heart induced by ligation of the left anterior descending coronary artery.

Table III. *Hemodynamic blood flows and heart rate before and after heart transplant in pigs*

			Stroke volume (ml/min)		*Cardiac output (ml/min)*		*Heart rate (beats/min)*
Time	*Animal*	*Condition*	*0 degrees*	*180 degrees*	*0 degrees*	*180 degrees*	
Before transplant	Donor	Baseline	3.4 ± 1.2	548 ± 141		162 ± 9	
	Recipient	Baseline	9.5 ± 4.0	912 ± 141		103 ± 10	
		Constricted	7.3 ± 5.1	845 ± 137		140 ± 10	
After transplant	Donor	Baseline	0.9 ± 0.2	1.4 ± 0.4	155 ± 40	234 ± 78	170 ± 10
		Constricted	0.5 ± 0.3	1.3 ± 0.3	91 ± 53	228 ± 48	160 ± 18
		V. Fib.		1.0 ± 0.2		132 ± 29	136 ± 35
	Recipient	Baseline	4.4 ± 0.7		753 ± 152		170 ± 9
		Constricted	3.1 ± 0.5		525 ± 109		160 ± 13

Data are mean ± standard deviation for five pigs before transplantation and three pigs after transplantation. Constricted, reduction of recipient aortic blood flow and pressure by 25% to 75% by constricting the ascending aorta; V.Fib., ventricular fibrillation of the recipient heart induced by ligation of the left anterior descending coronary artery.

dure, and 14 survived a minimum of 13 days (mean 18 days; range 13 to 29 days). Donor and recipient electrocardiograms rarely changed during the study; however, in three pigs, R-wave voltage in the donor heart declined, which prompted a suspicion of rejection that was confirmed histologically. Routine two-dimensional echocardiograms on days 4 to 6 in 16 pigs showed that donor contractility was normal in all, with antegrade flow through the biventricular outflow tract (Fig. 3). Valvular competence was present in all but one animal. Eight pigs underwent 10 additional echocardiograms for suspicion of rejection on postoperative days 5 to 29. Increased wall thickness, decreased diastolic compliance, or reduced ejection fraction were noted in five of the 10 studies. Rejection with gross areas of myonecrosis was confirmed by histologic study in all five.

For blood pool scans, separation of donor and recipient hearts in the five pigs studied was not difficult with appropriate septal views and when the epicardial electrocardiograms were used for gating. Donor cardiac output and ejection fraction were consistently less than recipient values (Table I). Rejection was not suspected in any of these pigs. Arteriography in two pigs demonstrated appropriate anatomic relations and forward blood flow from both hearts (Fig. 4, *A* and *B*).

Six late deaths occurred. They were caused by (1) infection in 4 pigs (pneumonia in one, empyema in one, and mediastinitis in two) and by perforation of the donor heart during angiography in one pig. The sixth death was unexplained.

Six pigs were long-term survivors with functioning donor hearts lasting more than 21 days. One had late echocardiographic findings suggestive of congestive heart failure in both hearts. Each pig was put to death electively and rejection was not present at necropsy in any of these pigs.

Phase III. Pretransplant hemodynamic data were obtained in all five recipients and donors. Posttransplant data were obtained in the three recipients that survived

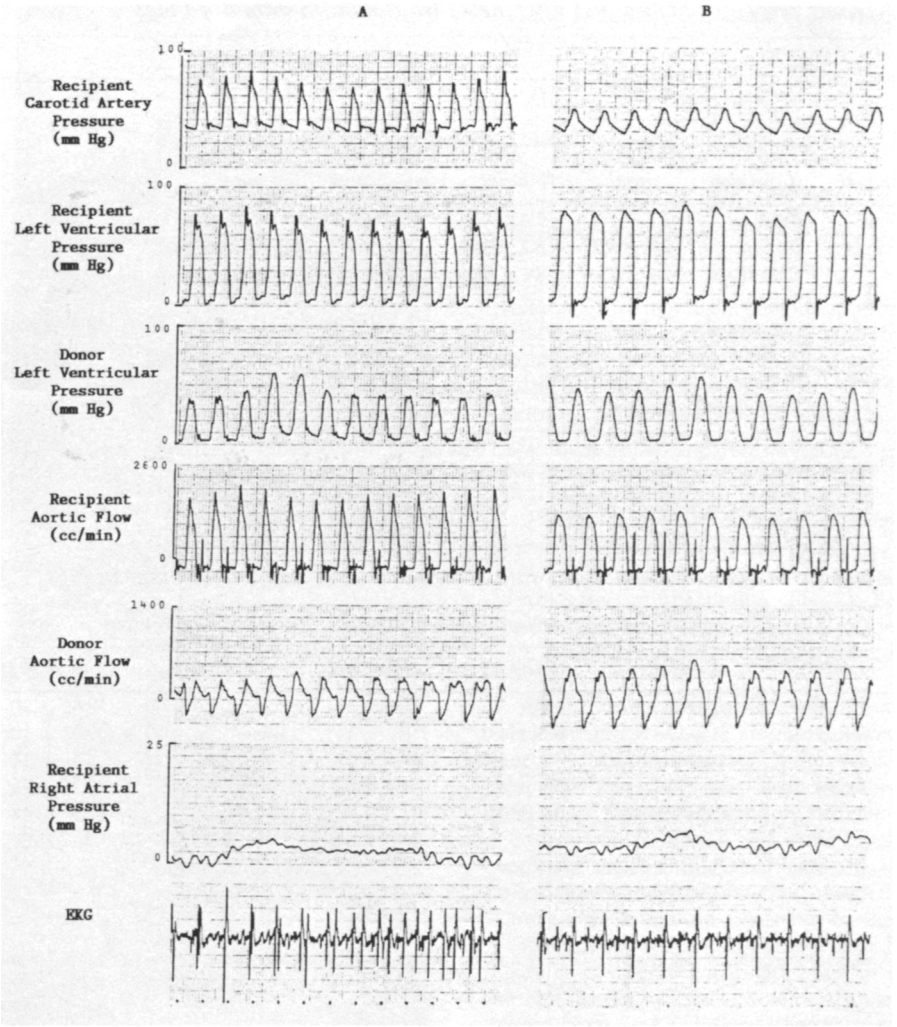

Fig. 5. Cardiovascular hemodynamics in an anesthetized pig after heterotopic heart transplantation. **A,** Hemodynamics during asynchronous beating of the donor and recipient hearts. Note that recipient pressures and flow are minimally affected by the donor heart. **B,** Hemodynamics during 25% to 50% constriction of the recipient ascending aorta. Note the increase in recipient left ventricular pressure, the decrease in ascending aortic flow and carotid artery pressure, and the increase in donor left ventricular pressure and donor aortic flow. *EKG,* Electrocardiogram.

the procedure. Of the other two recipients, one pig died as a result of the left ventricular catheter embolizing into the heart and one pig had severe acidosis refractory to treatment.

Pretransplant baseline pressures and flows in both the donor and the recipient were consistent with those reported in anesthetized neonatal and weanling pigs, respectively (Tables II and III).[11] When the ascending aorta in the recipient pig was partially constricted by an occluder, recipient left ventricular systolic and diastolic pressures and left atrial pressure all increased acutely. Stroke volume and cardiac output decreased while heart rate increased slightly (Table III).

Posttransplant baseline pressures and flow in the recipient were similar to pretransplant values, although stroke volume (9.5 to 4.4 ml) was lower and heart rate was higher (130 to 170 beats/min) (Tables II and III). The donor heart generated less left ventricular mean pressure (62.5 to 40 mm Hg) and flow (548 to 234 or 155 ml/min) after transplantation when it competed with the larger recipient heart. When the ascending aorta in the recipient pig was partially constricted, recipient left ventricular mean and end-diastolic pressures did not increase as much as during pretransplant constrictions because the donor heart was present. During significant constrictions of the recipient ascend-

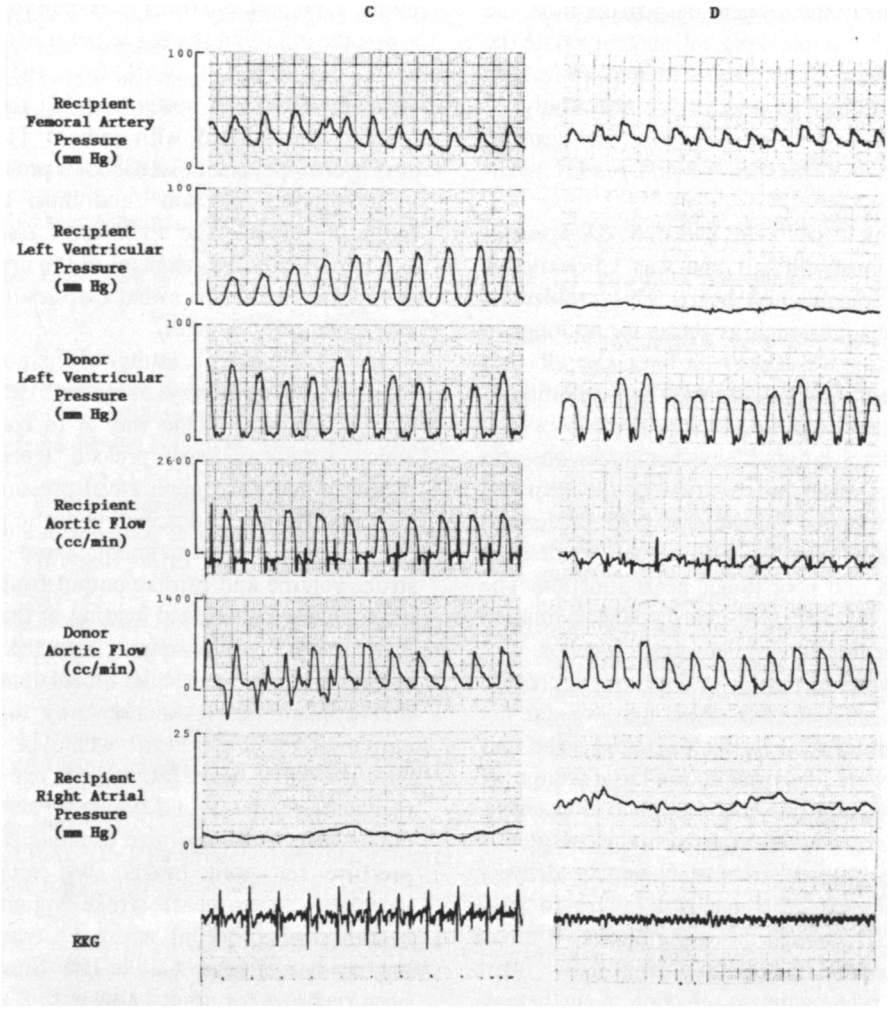

Fig. 5. Cont'd. Cardiovascular hemodynamics in an anesthetized pig after heterotopic heart transplantation. **C,** Hemodynamics during 50% to 75% constriction of the recipient ascending aorta. Note now the decrease in recipient left ventricular pressures and aortic flow, the increase in donor heart left ventricular pressure and donor aortic flow, and the generation of recipient femoral artery pressure that arises from the donor heart. **D,** Hemodynamics during ventricular fibrillation of the recipient heart. Note the donor heart generates all recipient femoral artery pressure and descending aortic blood flow.

ing aorta, the donor heart was able to assume a greater percentage of the overall cardiac output (Fig. 5, *A* to *D*), particularly when the donor heart beat 180 degrees out of phase with the recipient (Table III). During ventricular fibrillation of the recipient heart, the small donor heart was able to continue generating pressure and flow in the descending aorta of the recipient (Fig. 5, *C* and *D*).

Discussion

This investigation describes a new neonatal model of heterotopic heart transplantation in pigs and reports preliminary technical feasibility, immunosuppression, and hemodynamic results. Our model differs from previously reported models by the use of a single common atrium and a biventricular outflow tract in the donor, to bypass only the recipient left ventricle. This anatomic arrangement is possible in the newborn because the ventricles are functionally similar at birth. In adults, the donor right ventricle must be connected to the low-resistance pulmonary bed to prevent graft failure. Our model is also distinctive in that it allows for a size disparity as great as 3:1 between the recipient and donor because of its heterotopic position and because both the left and right ventricles contribute to the donor cardiac output.

The pig model was chosen because it is similar in size to newborn human infants and its coronary blood flow

physiology is similar to that of humans.[12] In addition, the thoracic cavity of the recipient pig will accommodate the smaller donor heart without excess lung compression. The pig is an established model for the study of transplant rejection and immunosuppression,[13] growth, and nutrition, and it is inexpensive and readily available.

Two major technical obstacles had to be overcome in this model. The most difficult one was coronary air embolism in the transplanted heart. This problem is particularly difficult inasmuch as there are no lungs in the donor circulation to absorb or filter the air that accumulates ex vivo. Careful attention to instillation of cardioplegic solution and to venting procedures has minimized this complication. The other major obstacle was effective myocardial preservation of the neonatal pig heart. A continuous infusion of cold crystalloid cardioplegic solution into the aortic root resulted in myocardial edema and poor donor heart function. The short, repeated infusions of cardioplegic solution described here resulted in excellent graft function.

Long-term survival of pigs given immunosuppressive drugs (phase II) was variable. Although we did not measure cyclosporine levels in this pilot study, the four infectious deaths were likely due to the large dosages of prednisone and cyclosporine that we gave. Conversely, transplant rejection, which occurred more frequently than expected, was probably due to inadequate delivery of the immunosuppressive drugs and failure to treat graft rejection early enough.[13] No pig died as a direct result of graft rejection. Since the normal native heart remained in situ, even complete rejection of the heterotopic heart did not result in death of the recipient.

Neither electrocardiograms nor two-dimensional echocardiograms were useful in noninvasive monitoring of rejection of heterotopic heart transplants. The electrocardiographic findings of reduced QRS voltage were insensitive and were abnormal only in the late stages of rejection. Our results supporting the inaccuracy of the electrocardiogram have been reported by others in both experimental and clinical studies.[14,15] Although we documented some of the previously described echocardiographic signals of rejection noted in adults, such as altered anatomic relations (wall thickness, left ventricular dimensions),[16] left ventricular diastolic function,[17] left ventricular systolic function,[18] and acoustic properties,[19] rejection was not consistently documented by any single echocardiographic index in this neonatal model.

Gated technetium 99m red cell blood pool scans were able to quantitate cardiac output and ejection fraction independently in both donor and recipient hearts in the five transplants examined. Thus gated scans may be useful in heterotopic transplantation to semiquantatively assess the ability of the donor heart to assume all or part of the hemodynamic work from the failing recipient ventricle. However, newer imaging techniques such as lymphocytes labeled with indium 111 or radioactive antimyosin monoclonal antibodies promise better results in monitoring rejection[20] and must be studied in an immature model. The noninvasive assessment of rejection is particularly important in the immature recipient, as repeated endomyocardial biopsies may be dangerous and technically difficult.

The preliminary results of hemodynamic studies (phase III) suggest ways to increase cardiac output from the smaller heart. One way is to constrict the aorta, which would increase preload (recipient left atrial pressure, donor common atrial pressure), and decrease afterload (recipient descending aortic pressure) (Tables II and III). In our experiments, these changes increased stroke volume and cardiac output from the donor heart despite nonsynchronized beating of the two hearts (Fig. 5, *A* to *D*). Cardiac output from the donor heart also increased when ventricular fibrillation was induced in the recipient heart. Another way to increase cardiac output of the donor heart would be to synchronously pace the donor heart 180 degrees out of phase with the recipient, which would decrease systolic afterload for the donor heart and maximize diastolic coronary perfusion pressure for both hearts. We repeatedly observed increased donor heart stroke volume and therefore overall cardiac output when the two hearts beat 180 degrees out of phase (Table III). Similar findings have been reported for adult baboons.[4]

Partial cardiac augmentation or substitution with a heterotopic heart transplant would theoretically be appealing in a variety of currently uncorrectable conditions, if immune tolerance is improved in very immature donor tissues and if long-term survival, growth, and development can be documented. These conditions include left-sided cardiac lesions such as some forms of hypoplastic left heart syndrome, mitral valve atresia, and severe aortic atresia,[10] which, although relatively rare, still collectively account for significant morbidity and mortality. Other congenital heart lesions, such as hypoplastic right heart syndrome, pulmonary atresia, and single ventricle, could also benefit from this type of transplant technique. Expanded use of limited organ tissue would also be possible because greater discrepancies in size match between donor and recipient would be tolerated.

Despite the many theoretical advantages of heterotopic over orthotopic heart transplantation for congenital heart disease, this procedure must be further devel-

oped and adequately tested in animal models and the pathophysiology and hemodynamics must be experimentally defined before consideration of clinical applications in humans.

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Discussion

Dr. Vaughn Starnes *(Stanford, Calif.).* The authors should be congratulated for introducing an applicable model for studying neonatal allograft rejection. Their work also provides us with an opportunity to look at a model for the study of growth and development of the immature heart after transplantation. I do have some reservations about its clinical applicability, and I would like to make some opening comments and then ask Dr.Verrier two questions.

The experimental model proposes to place the allograft in a heterotopic position, distal to the frequently occurring coarctation site. The anatomic studies of the hypoplastic left heart syndrome have revealed a 70% to 80% coarctation rate. Therefore, the proposed experimental model, if used clinically, would not address the issue of the critical coarctation that would make retrograde perfusion of the coronary arteries and cerebral vessels problematic. Because the hypoplastic heart has a very small left atrium, I believe doing this operation without bypass in a clinical setting would be virtually impossible.

I would like to ask Dr. Verrier if he believes this experimental model is clinically applicable for the hypoplastic left heart syndrome.

Dr. Verrier. The spectrum of hypoplastic left heart syndrome is wide. The presence of an aortic coarctation does not by itself limit applicability inasmuch as the coarctation repair could be incorporated in the aortic anastomosis. We are not proposing this model for clinical treatment of hypoplastic left heart syndrome presently. However, the clinical results with this anomaly have been so dismal with the palliative Norwood procedure in most surgeons' hands that this type of heterotopic transplantation technique may be applicable. In the severe right-sided hypoplastic lesions, there has been a recent propos-

al by the group at the University of California at Los Angeles to use a heterotopic transplant as augmentation.

Dr. Starnes. Dr. Verrier has devised a model in which the right ventricle and left ventricle are functioning in synchrony. The issue of donor availability again arises. If this model is applied in neonates, then the hemodynamic pressures in the right and left ventricles are almost identical in the newborn period, and the muscle wall thickness of the right ventricle does not regress. Beyond the newborn period, for instance, at 14 to 18 days, then right ventricular or left ventricular regression begins to occur, as demonstrated by the recent literature on arterial switch procedures. Dr. Verrier, are there limitations of using this particular model in neonates because of the inadequate number of donors?

Dr. Verrier. Donor availability is the ultimate question for any transplantation procedure in adults and particularly in children. Transplantation will never be an alternative unless donor resources are improved. Whether or not this heterotopic approach extends the ability to use donor resources is conjecture. We have been able to put small hearts into larger animals. What we have not determined yet is the size required to truly compensate for a failing left ventricle. I think some additional benefits are accrued by having both ventricles working through the biventricular outflow tract, and that opens up the size range a bit. If anencephalic infants ultimately become sources of donor tissues and the diagnosis is made prenatally, optimal matching of donors and recipients may be possible in early infancy. Heterotopic cardiac transplantation might improve the use of such a resource.

Dr. Starnes. One final question. Would Dr. Verrier and his group see this as a model for a biologic left ventricular assist, more so than heart replacement?

Dr. Verrier. Yes. In most congenital lesions, the right ventricle is the more vulnerable ventricle; there are not that many congenital left ventricular lesions requiring augmentation. However, this model works very well as a ventricular assist and works even better when the heart is paced out of phase. Similar augmentation has been done experimentally by Lousman and associates in adult baboons and has worked well.

For transplantation to become a widely established therapeutic alternative in children, simpler immature experimental models must be developed. Our work represents such an attempt.