Lung and heart-lung transplantation: the state of the art

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■ Lung and heart-lung transplantation is one of the most rapidly evolving transplantation fields. Survival has been improving with better patient selection, better graft preservation, and better immunosuppression. This paper outlines criteria for patient selection, reviews the surgical options involving lung transplantation, and discusses factors influencing morbidity and survival in these patients. The Cleveland Clinic Foundation experience with these procedures is presented. Lung and heart-lung transplantation has emerged from the experimental realm to the therapeutic, and can now be offered as an effective treatment option to many patients with previously fatal heart and lung disorders.

□ INDEX TERM: HEART-LUNG TRANSPLANTATION, LUNG TRANSPLANTATION □ CLEVE CLIN J MED 1992; 59:307–316

TRANSPLANTATION of the lungs was first successfully performed during the 1980s. Since then, this procedure has become one of the most rapidly evolving in the field of transplantation. The earliest clinical attempts at lung and heart-lung transplantation were made nearly 30 years ago.

See Theodore, p 330

In 1963, James Hardy at the University of Mississippi transplanted the left lung of a patient with squamous cell carcinoma.[1] The patient died of renal failure 18 days later. Over the next 20 years, approximately 40 lung transplants were performed, with dismal results. Only one patient survived hospitalization,[2] and that patient died 10 months after transplantation surgery.

Denton Cooley performed the first heart-lung transplant on a 2-month-old patient with atrioventricular canal in 1968.[3] This patient died soon after surgery. Two more unsuccessful heart-lung transplants were performed before Bruce Reitz successfully performed the operation on a patient with primary pulmonary hypertension in 1981.[4]

The clinical failures of the 1960s and 1970s reflected poor patient selection, inadequate lung preservation, excessive immunosuppression (pre-cyclosporine), limited understanding of the physiology of the transplanted lung, and the need for specialized postoperative care. With better patient selection, techniques, and immunosuppression, results have improved, and the number of transplants performed has been increasing (*Figure 1*).

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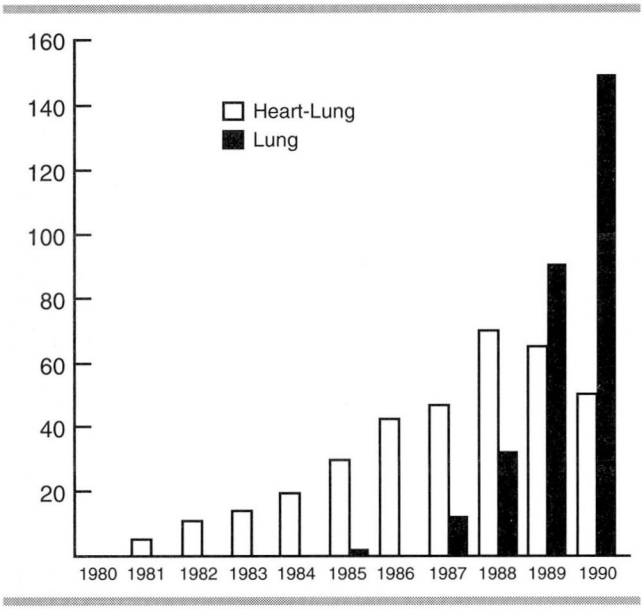

FIGURE 1. In the United States, the number of heart-lung transplants performed plateaued at approximately 60 per year. With improving results, however, the number of lung transplants performed each year is increasing and exceeds 150 per year in the early 1990s.

TABLE 1
CRITERIA FOR LUNG TRANSPLANTATION

Indications for transplant
Single-lung transplant
Pulmonary fibrosis (idiopathic or secondary)
Emphysema
Primary pulmonary hypertension
"Correctable" Eisenmenger's syndrome (eg, atrial septal defect, patent ductus arteriosus, ventricular septal defect)
Bronchopulmonary dysplasia
Lymphangioleiomyomatosis
Histiocytosis X
"Bilateral" lung transplant
Cystic Fibrosis
Bronchiectasis
Bullous Emphysema
Heart-lung transplant
"Complicated" Eisenmenger's syndrome (eg, atrioventricular canal, transposition of the great arteries, truncus arteriosus)
Contraindications to transplant
Absolute
"Physiologic" age >60 years
Malignancy
Systemic disease
Current smoker
Relative
Ventilator dependent
Steroid use
Previous cardiothoracic surgery
Noncompliance history
"Too sick"

TABLE 2
SURGICAL OPTIONS FOR LUNG TRANSPLANTATION

Single-lung transplant (right or left, with cardiopulmonary bypass if needed
Single-lung transplant with congenital heart defect repair
Bilateral (double) lung transplant
Heart-lung transplant (one or both lungs)
Living-related donor lung transplant
Reduced-size lung transplant (unrelated donor)

TRANSPLANTATION CRITERIA

Indications

Patients with end-stage pulmonary disease are candidates for lung transplantation. Patients with end-stage cardiac and lung disease are candidates for heart-lung transplantation. Transplantation has been performed for a wide variety of pulmonary and cardiac conditions (*Table 1*). Pulmonary fibrosis (either idiopathic or secondary to other causes) has been successfully treated with single-lung transplantation.[5] With growing experience, single-lung transplantation has been extended to patients with emphysema (especially due to alpha-1-antitrypsin deficiency), primary pulmonary hypertension, and Eisenmenger's syndrome with congenital heart defects that can be repaired during the transplantation procedure (eg, atrial septal defect, patent ductus arteriosus, ventricular septal defect).[6–11]

Patients with complicated congenital heart defects and Eisenmenger's syndrome (eg, atrioventricular canal, transposition of the great arteries, truncus arteriosus) can be treated with heart-lung transplantation.[12] Patients with "irreversible" cardiac dysfunction secondary to pulmonary hypertension also may require heart-lung transplantation, but criteria to determine reversibility are currently not fully defined.

Patients with "septic" lung disease (eg, cystic fibrosis, bronchiectasis) require replacement of both lungs to avoid contamination of the transplanted lung from a nontransplanted, infected lung, and this has been successfully performed with either double-lung or heart-lung transplantation.[13,14]

Contraindications

Currently, the lower age limit for heart-lung and lung transplantation is not well-defined. At Stanford, successful transplantation has been performed in children less than 1 year old. The upper age limit depends upon "physiologic" age rather than chronologic age.

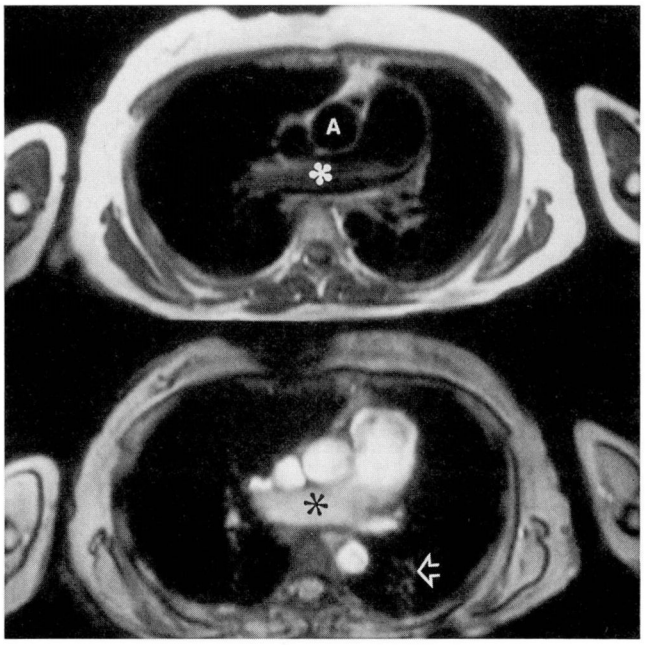

FIGURE 2. Preoperative pulmonary arterial condition in a patient with pulmonary arterial hypertension (spin-echo and cine; transaxial). Compared to the normal-sized ascending aorta (A), the pulmonary arteries are significantly dilated. Abnormal systolic intravascular signal patterns, representing slow blood flow, are best demonstrated within the right central pulmonary artery (asterisks). Specifically, abnormal signal increase, compared to the normal signal void in the aorta is noted on the spin-echo image [above]. Flow signal in the descending left pulmonary artery (open arrow) is minimal.

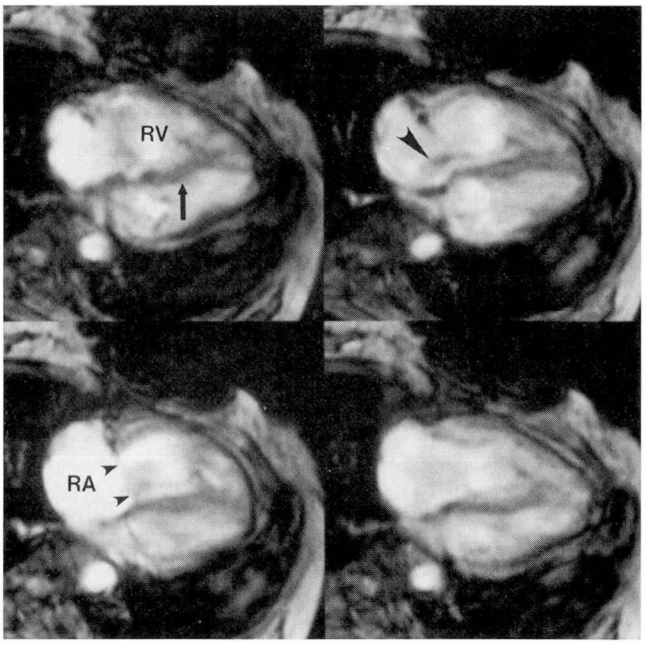

FIGURE 3. Four representative images (cine;four-chamber view) from the cardiac cycle of the patient in *Figure 2* demonstrate the following: dilatation and hypertrophy of the right ventricle (RV) with flattening of the interventricular septum (arrow); diminished contraction of the right ventricle from end-diastole (above-left) to end-systole (below-left); and systolic signal-void jet (large arrowhead) of mild regurgitation passing from the level of the tricuspid valve (small arrowheads) into the right atrium (RA).

Generally, age 60 is the preferred limit, but occasional vigorous patients in their 60s have undergone transplantation successfully.

Absolute contraindications to heart-lung and lung transplantation are similar to those for other solid-organ transplants (*Table 1*). Patients with malignancy or a recent history of malignancy are not eligible. Patients with systemic infection, or active infection other than in the lung, are also excluded. However, patients with cystic fibrosis or bronchiectasis, in which the infection is confined to the lungs, are eligible since the source of infection is completely removed at operation. Also, patients with other organ dysfunction from systemic disease (eg, lupus erythematosus, scleroderma, and insulin-dependent diabetes with end-organ dysfunction) are excluded. Finally, patients with emphysema, or any other cardiopulmonary condition, who continue to smoke should not be considered.

A variety of relative contraindications are assessed on an individual basis. Ventilator-dependent patients are usually not acceptable for transplantation because of nosocomial infection and wasting of the respiratory muscles, which can make postoperative extubation very difficult. An occasional ventilator-dependent patient has successfully undergone transplantation when time on the ventilator was brief and no lung infection was present. Use of steroids has been an absolute contraindication in the past, but recently patients have undergone successful transplantation without bronchial healing problems despite the use of preoperative steroids.[8] The steroid dosage should be eliminated or minimized before transplantation.

Previous cardiothoracic surgery may cause problems, especially for heart-lung transplantation. In these cases, the extensive dissection and lengthy duration of cardiopulmonary bypass may lead to fatal postoperative bleeding. Currently, patients with previous surgery are reviewed on a case-by-case basis. As with all transplant operations, patient compliance and psychosocial back-

TABLE 3
RV FUNCTION BEFORE AND AFTER SINGLE-LUNG TRANSPLANTATION

	RV EF	RV EDV (mL)	RV ESV (mL)	SV (mL)	CI (L/min/m^2)
*2 mo pretransplantation	25%	113	85	28	NA
OR (pretransplantation)	23%	181	140	41	2.5
OR (posttransplantation)	47%	136	95	41	2.5
0-12 hr posttransplantation	46%	63	35	28	2.2
12-24 hr posttransplantation	47%	56	30	26	2.0
24-48 hr posttransplantation	45%	101	56	45	3.1
48-72 hr posttransplantation	45%	126	72	54	3.1
*1 mo posttransplantation	71%	98	28	70	NA

*Determined by cardiac magnetic resonance imaging.
Determined by thermodilution RVEF catheter (Baxter-Edwards Laboratories; Santa Ana, California[11])
RV, right ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; CI, cardiac index; NA, not available using MRI; OR, in operating room

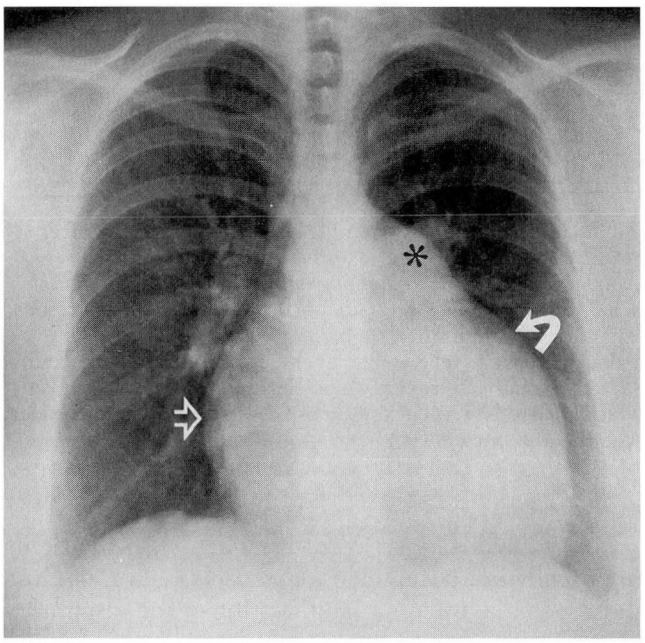

FIGURE 4. Plain-film appearance of severe pulmonary arterial hypertension (Eisenmenger's syndrome) with right heart failure demonstrating marked increase in the size of the cardiac silhouette. The main pulmonary artery segment (asterisk) and hilar shadows of the central pulmonary arteries are large. Right heart failure is manifested by prominence of the right atrial border (open arrow) and right-ventricular outflow tract (curved arrows).

ground are critically important. Noncompliance after transplantation is a form of "passive suicide"; thus, a history of previous noncompliance is a cause for concern. In addition, strong family support is essential for these patients, who require frequent postoperative visits, and perhaps rehospitalization.

Patients with end-stage problems may deteriorate during the wait before transplantation. Transplantation for debilitated end-stage patients is usually unsuccessful because the patients do not have the stamina to withstand the rigorous postoperative course. Therefore, some patients become "too sick" and cannot undergo transplantation.

SURGICAL OPTIONS

In the past 2 years, a variety of new approaches to lung and heart-lung transplant (*Table 2*) have been used. The most rapid expansion has been with single-lung transplantation, which can be performed to either the right or left lung. During the operation, cardiopulmonary bypass may be required for recipients with elevated pulmonary artery pressures or severe hypoxemia. If a congenital heart defect is to be repaired at the same time, this dictates the approach to surgery. For atrial septal defect and ventricular septal defect, we would plan for right-lung transplantation, with closure of the defect through the right thoracotomy. For patent ductus arteriosus, a left thoracotomy with left-lung transplantation and repair of the defect can be performed simultaneously.

Double-lung transplantation

Double-lung transplantation is primarily indicated for patients with septic lung conditions such as cystic fibrosis or bronchiectasis. In addition, patients with bullous emphysema may be best served by a double-lung procedure. In single-lung transplantation for bullous disease, overinflation of the native lung may lead to compression of the transplanted lung. Previously, double-lung transplantation was performed on cardiopulmonary bypass through a median sternotomy with tracheal, left atrial, and main pulmonary artery anastomoses; however, results were disappointing, with a high risk for airway complications and early death.[14] A more recent operation with "bilateral" lung transplantation has been much more successful and may be performed without the use of cardiopulmonary bypass.[15]

Heart-lung transplantation

Heart-lung transplantation was performed for a variety of conditions during the 1980s. Because of the

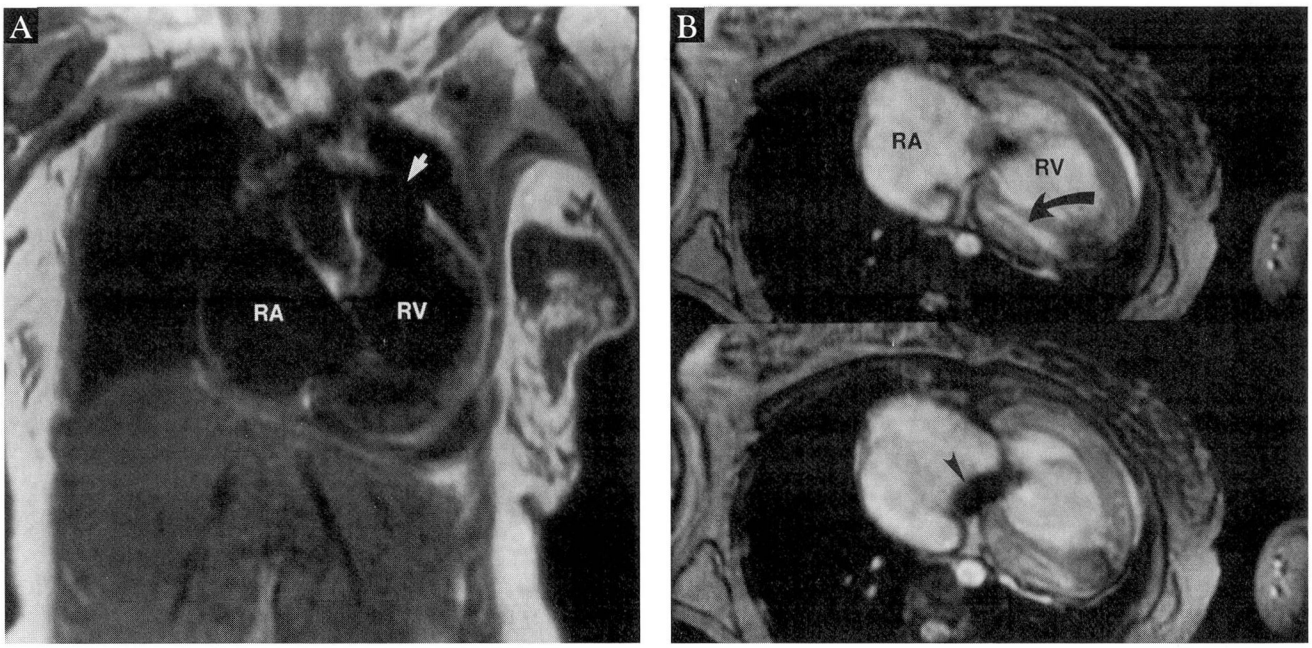

FIGURE 5. Anatomic and functional MRI evaluation of right heart failure in the patient illustrated in *Figure 4* (A: static spin-echo: coronal; B: dynamic cine: four-chamber view). The coronal anatomic image clearly shows the marked dilatation of the right atrium (RA), right ventricle (RV), and main pulmonary artery (arrow), accounting for the plain-film appearance in *Figure 4*. The end-diastolic (above) and mid-systolic (below) images from the dynamic cine loop demonstrate both structural and associated functional abnormalities, including: poor contractility of the dilated and hypertrophic right ventricle; abnormal compressed, slit-like appearance of left ventricle (curved arrow); and systolic signal-void jet (arrowhead) of significant tricuspid regurgitation.

shortage of donor organs, the number of heart-lung transplant operations performed has been very limited, and many patients die awaiting surgery.[16] With the success of single-lung transplantation during the late 1980s, indications for the combined heart-lung procedure have narrowed. Currently, patients with complicated congenital heart defects and Eisenmenger's syndrome are the most well-defined group requiring replacement of both heart and lungs. Selected patients with cardiomyopathy and severe pulmonary hypertension may be heart-lung transplantation candidates.

Some centers perform "domino" heart-lung transplantation for cystic fibrosis and emphysema patients.[13] In this case, the heart-lung recipient's heart is removed and transplanted into a patient awaiting heart transplantation.[17] This makes better use of the organs, but leaves the heart-lung recipient susceptible to the complications of heart transplantation. Therefore, with the recent success of "bilateral" lung transplantation,[15] the trend is to perform a bilateral procedure rather than domino heart-lung transplantation. Combined transplantation of the heart and a single lung has been performed in rare cases of patients who need heart-lung transplantation but who have extensive adhesions unilaterally.[18] This avoids the technical problems and bleeding that could complicate the dangerous pleural dissection.

Living-related donor transplantation

In October 1990, the first living-related donor single-lung transplantation was performed at Stanford. In this operation (Vaughn A. Starnes, Stanford, California, personal communication) a 12-year-old patient with bronchopulmonary dysplasia received a right upper lobe donated by the patient's mother. The mother's upper lobe fit well into the child's right chest and both patients have made an excellent early recovery. It is hoped that lung rejection will be less of a problem using a related donor. A subsequent patient, a 1-year-old, underwent reduced-size lung transplantation[19] using a lobe from an older, unrelated donor (Vaughn A. Starnes, personal communication). These new operative approaches offer additional hope for pediatric recipients for whom the donor shortage is particularly threatening.

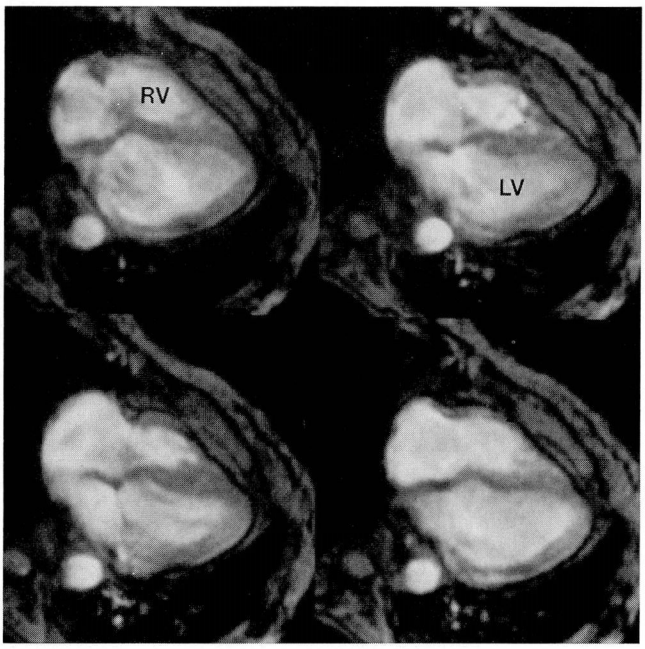

FIGURE 6. Three-month postoperative cardiac condition (cine; four-chamber view). Four representative images corresponding to those in *Figure 3* demonstrate the following: decrease in size of the right atrium and right ventricle (RV) which shows evidence of improved ventricular function; normal appearance of the left ventricle (LV) and interventricular septum; and absence of a jet of tricuspid regurgitation.

HEART-LUNG vs SINGLE-LUNG TRANSPLANTATION: CONTROVERSY

For many reasons, the momentum in recent years has been to perform single-lung rather than heart-lung transplantation. The donor shortage of heart-lung transplant grafts is severe. Donor hearts are first offered to "status I" heart transplant patients, and there are usually several status I heart transplant patients with a higher priority than heart-lung candidates.[16] Competition for the donor heart does not exist with patients waiting for single or bilateral lung transplantation. The lungs can be removed from a donor separate from the heart, leaving acceptable "cuffs" for heart and lung transplantation (right, left, or both).[20] The potential thus exists to perform heart, right-lung, and left-lung transplantation to three separate recipients from a single donor. This makes more efficient use of donor organs than a single heart-lung transplant graft for one recipient. Furthermore, some argue that scarce donor hearts are better utilized for orthotopic cardiac transplantation with a "predictable" survival, rather than the 59% 1-year survival obtained by most heart-lung transplant programs.[21]

Until recent years, the morbidity and mortality of single- and double-lung transplantation were higher than for the heart-lung procedure. Now that the early posttransplantation survival of these three operations is roughly equal, the long-term risk for complications of the transplanted heart in the heart-lung transplant operation has become an issue. The morbidity of cardiac denervation, cardiac rejection, and accelerated arteriosclerosis of the transplanted coronary arteries (which affects approximately 50% of patients 5 years after heart transplantation[22]) limit the long-term functional results and survival.

Recovery of cardiac function

Much of the current controversy regarding patient selection for lung vs heart-lung transplantation concerns the recovery of cardiac function after lung transplantation. Patients with primary or secondary pulmonary hypertension develop pulmonary arterial dilatation with diminished intravascular flow (*Figure 2*). Secondary effects on the heart include right ventricular hypertrophy and dilatation, tricuspid regurgitation, decreased right ventricular ejection fraction, and bowing of the ventricular septum into the left ventricle (*Figure 3*). With progression of the disease, patients will develop additional right heart failure, resulting in hepatomegaly, ascites, pedal edema, and liver function abnormalities (*Figures 4* and *5*). Early results suggest that cardiac recovery and remodeling can proceed at a rapid rate, with nearly complete recovery of cardiac function after single-lung transplantation (*Figures 6* and *7*). *Table 3* demonstrates the improvement of right ventricular function seen in our third transplant patient, and illustrated in *Figures 2, 3, 6,* and *7*.

Some unanswered questions

Many questions regarding the proper selection of patients for heart-lung or lung transplantation are unanswered. How much cardiac recovery can be anticipated after lung transplantation, and how soon after the operation? Can lung transplantation be safely offered to patients with severe clinical right heart failure? What functional recovery can be expected for these patients? What is the best means of evaluating cardiac function before and after transplantation?

Although these questions are not categorically answered, clinical results of lung transplantation have been encouraging. Because of the shortage of donor

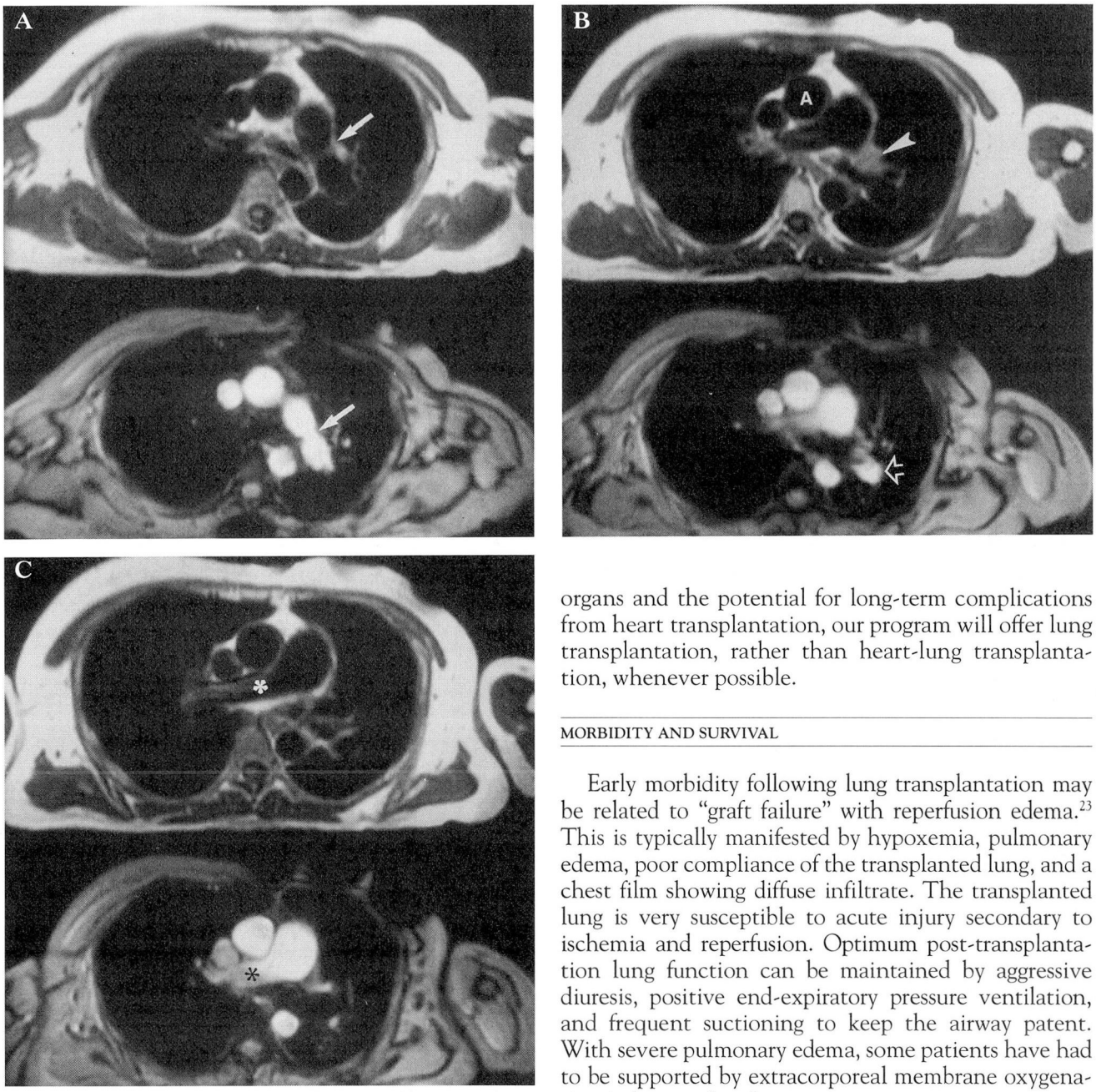

FIGURE 7. Three-month postoperative pulmonary arterial condition (spin-echo and cine; transaxial). Three pairs of images (7A = most cranial, 7B = intermediate level, 7C = most caudal) corresponding to those in *Figure 2* demonstrate the following: improvement in the size of the main and central pulmonary arteries compared to the ascending aorta (A); patency of the left central pulmonary artery anastomosis (arrows) with the surrounding intermediate-intensity muscle flap (arrowheads); and improved flow signal in the left central pulmonary artery including the descending branch (open arrows), and in the right central pulmonary artery [asterisks].

organs and the potential for long-term complications from heart transplantation, our program will offer lung transplantation, rather than heart-lung transplantation, whenever possible.

MORBIDITY AND SURVIVAL

Early morbidity following lung transplantation may be related to "graft failure" with reperfusion edema.[23] This is typically manifested by hypoxemia, pulmonary edema, poor compliance of the transplanted lung, and a chest film showing diffuse infiltrate. The transplanted lung is very susceptible to acute injury secondary to ischemia and reperfusion. Optimum post-transplantation lung function can be maintained by aggressive diuresis, positive end-expiratory pressure ventilation, and frequent suctioning to keep the airway patent. With severe pulmonary edema, some patients have had to be supported by extracorporeal membrane oxygenation in hopes of graft recovery.

Rejection

Lung rejection is commonly seen approximately 7 to 10 days following transplantation. Clinically, it is manifested by low-grade fever, tachypnea, dyspnea, hypoxemia, and chest films showing infiltrates with pleural effusion (*Figure* 8, A). Histologically, lung rejection is characterized by perivascular infiltrates of mononuclear cells.[24] In general, episodes of lung rejec-

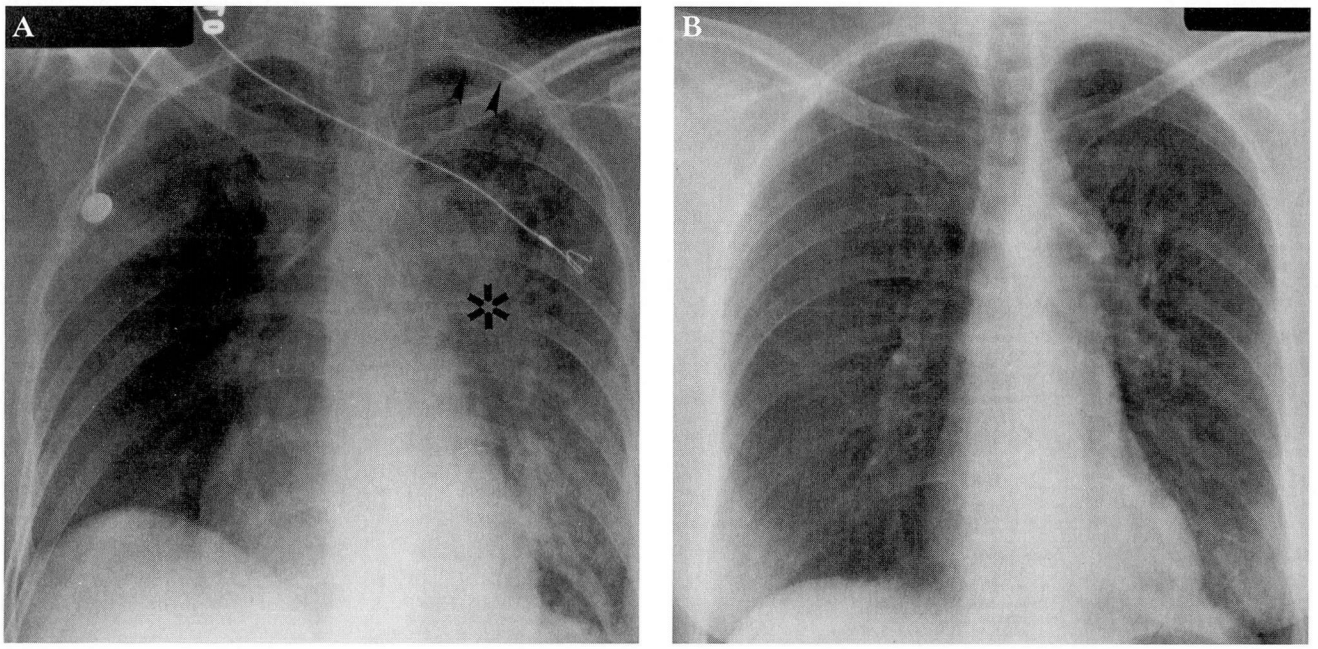

FIGURE 8. Typical chest film findings with left lung rejection (A) consisting of perihilar consolidation (asterisk) and posteriorly layering pleural effusion (arrowheads). Following a 3-day pulse of methylprednisolone, both clinical and plain-film evidence of improvement were noted (B).

tion respond well to pulsed doses of methylprednisolone (*Figure 8, B*). Polyclonal T-cell antibody (ATG), monoclonal CD3 antibody (OKT3), and total lymphoid irradiation have also been used for the treatment of lung rejection episodes.

Infection

The lung is the only transplanted solid organ continuously exposed to environmental conditions. Therefore, infection of the transplanted lung is not uncommon, especially during the early postoperative course, when the patient is susceptible to nosocomial infections. The clinical situation (fever, hypoxemia, lung infiltrates) makes it difficult to distinguish rejection from infection. Therefore, transbronchial lung biopsy, directed by fluoroscopy, and transbronchial lung washings are performed in order to clarify the issue.[25]

Anastomotic dehiscence

Dehiscence of the bronchial or tracheal anastomosis was a major cause of death in early lung transplant operations.[2] With the use of omentum, either to wrap around the bronchial anastomosis and provide blood supply or to seal small bronchial leaks, the problem diminished. We currently use a pedicle of intercostal muscle to wrap the bronchial anastomosis and avoid the need for a separate abdominal incision to mobilize the omentum.

Late complications

Late complications following lung transplantation include those associated with immunosuppression (eg, hypertension, renal failure, osteoporosis, malignancy). In addition, one late complication specific to lung transplantation is obliterative bronchiolitis.[26] This is manifested by declining pulmonary functions (especially FEF^{25-75}) and is characterized histologically by fibrotic plugging of the terminal bronchioles. The incidence and severity of obliterative bronchiolitis may be decreasing in recent years.[12] Much basic and clinical research is still needed to better understand and treat this clinical problem.

Survival

Results of heart-lung transplantation were improving substantially by the late 1980s.[12] This was primarily due to a "learning curve" (*Figure 9*) and may reflect the use of triple-drug immunosuppression (cyclosporine, prednisone, azathioprine) introduced in 1986. Recently, 75% survival at 1 and 2 years has been attained, with most of the mortality occurring during the early postoperative phase. Survival following single-lung

transplantation is even more remarkable. Until 1983, only one patient survived the hospitalization. Currently, 78% 1-year, and 74% 2-year survival rates have been reported.[27] Results following "bilateral" single-lung transplantation should be in the same range (J.D. Cooper, personal communication).

TABLE 4
CLEVELAND CLINIC FOUNDATION LUNG TRANSPLANT PATIENTS

	Age/sex/diagnosis	Waiting list	Procedure	Outcome
1.	44 M Pulmonary fibrosis with pulmonary hypertension	12 days	Left lung transplant	Well
2.	24 F Eisenmenger's syndrome	25 days	Atrial septal defect repair/ Right lung transplant	Well
3.	44 F Primary pulmonary hypertension	89 days	Left lung transplant	Well
4.	56 F Emphysema	3 days	Left lung transplant	Well
5.	38 F Eisenmenger's syndrome	141 days	Patent ductus arteriosus division; left lung transplant	Died

The CCF program

In the first 8 months of the Cleveland Clinic Foundation Heart-lung and Lung Transplantation program, 54 patients ranging in age from 2 months to 70 years were referred for lung or heart-lung transplantation, 15 of whom were accepted for lung transplantation (12 single-lung, 3 bilateral). Of these 15 patients, 3 died while awaiting surgery, and 7 remain on the waiting list. Five patients underwent lung transplantation (*Table 4*). Of these 5 patients, 4 would have undergone heart-lung transplantation by previous criteria (some were waiting for heart-lung transplantation at other programs). Four of these patients are alive and well, but 1 patient died early postoperatively due to acute lung graft failure. All 4 survivors no longer require supplemental oxygen and have returned to full activities. One patient with atrioventricular canal is awaiting heart-lung transplantation.

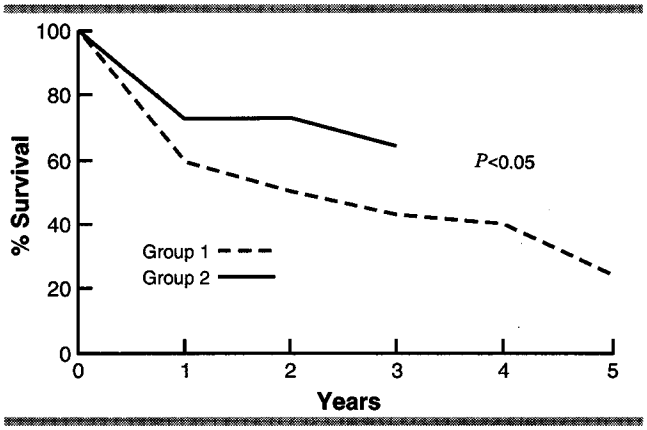

FIGURE 9. Survival following heart-lung transplant at Stanford University. Group 1 underwent transplant from 1981 to 1986; group 2 (from 1986 through April 1989) demonstrated improved survival ($P < 0.05$). Reproduced with permission from McCarthy PM, Starnes VA, Theodore J, et al.[1]

FUTURE ISSUES

It may be expected that the shortage of donors will severely limit the number of lung transplant procedures that can be performed, probably to a maximum of 300 to 400 per year. (This figure is based on the assumptions that 1,700 heart transplant procedures per year will be performed in the United States, that 15% of the donors will have acceptable lung function for donation,[28] and that some donor lungs will be used for bilateral lung transplantation, and others for separate right- and left-lung transplant procedures.) Living-related donor and reduced-size lung transplantation may be an option for children, since the donor shortage is particularly severe for that group. Theoretically, with the use of related donors, rejection may be less frequent and severe, but better preservation of the lung graft than our current techniques permit is necessary in order to obtain the more predictable early results seen following other solid-organ transplant operations. The limits of extending single-lung transplantation to patients with secondary right-heart dysfunction will need to be more clearly defined. Finally, a host of new immunosuppressive agents (FK506, RS-61443, Rapamycin, and monoclonal antibodies) should offer exciting new advances in all fields of transplantation.

Lung and heart-lung transplantation is one of the most rapidly evolving fields in transplantation. With better patient selection, better graft preservation, and better immunosuppression, survival of lung and heart-lung transplant recipients is approaching that seen in heart and other solid-organ transplant recipients. Lung and heart-lung transplantation has emerged from the experimental realm to the therapeutic and can now be offered as an effective treatment option to many patients with previously fatal heart and lung disorders.

ADDENDUM

As of September, 1991, the Cleveland Clinic Foundation Lung Transplant Program has performed 16 transplants (13 single-lung, 3 double-lung) with 12 survivors (75%). Twelve patients are waiting for lung transplant. Two patients were waiting for heart-lung transplant; one has died while waiting.

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