COMBINED LUNG AND LIVER TRANSPLANTATION IN PATIENTS WITH CYSTIC FIBROSIS

A 4½-year experience

Patients with cystic fibrosis who have end-stage respiratory failure and associated liver cirrhosis have been considered poor candidates for lung transplantation because of high morbidity and mortality resulting from hepatic insufficiency after the operation. Since April 1989, our policy has been to combine heart-lung or lung and liver transplantation in this group of patients. Between June 1990 and March 1995, among 25 patients accepted in the program for combined transplantation, nine died awaiting transplantation and 10 underwent one of the following procedures: heart-lung-liver transplantation ($n = 5$), en bloc double lung-liver transplantation ($n = 1$), sequential double lung-liver transplantation ($n = 3$), and bilateral lobar lung transplantation from a split left lung and reduced liver transplantation ($n = 1$). There were 5 male and 5 female patients. The ages of the recipients ranged from 10 to 24 years. Mean forced expiratory volume in 1 second was 29% and mean forced vital capacity was 35% of predicted values. All patients were infected with resistant *Pseudomonas*, three with *Pseudomonas cepacia*, and two patients had *Aspergillus* species in addition. All patients had severe cirrhosis with portal hypertension. Four patients had a history of esophageal variceal bleeding and two had had previous portosystemic shunts. The operation was performed as a two-stage procedure, the intrathoracic operation being completed before the abdominal stage was begun. Cardiopulmonary bypass was used in all patients because of poor clinical condition. Immunosuppression consisted of azathioprine, cyclosporine, and prednisone, as for isolated lung transplantation. There were two perioperative deaths, one caused by primary liver failure and the second by early lung dysfunction. For the first 3 months after transplantation pulmonary infection was the most common cause of morbidity. Other complications included tracheal stenosis ($n = 1$), bronchial stenosis ($n = 1$), biliary stricture ($n = 2$), and severe ascites ($n = 3$). All were successfully treated. Obliterative bronchiolitis developed in three patients. This was stabilized with FK 506 in two patients; the other patient underwent retransplantation at 38 months but eventually died of bleeding. Actuarial survival was 70% at 1 year and remained unchanged at 3 years. Significant functional improvement was observed in all survivors. For patients who have chronic respiratory failure with advanced cirrhosis, lung transplantation combined with liver transplantation can be performed with a satisfactory outcome. (J THORAC CARDIOVASC SURG 1995;110:1415-23)

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Cystic fibrosis (CF) is a multisystem genetic disease carried by 5% of the population. It is characterized by widespread disturbance of electrolytic transport and protein excretion in exocrine glands. Pulmonary disease, exocrine pancreatic insufficiency with malabsorption, and diabetes mellitus are frequently present in patients with CF.¹ Despite new therapies such as uridine triphosphate, deoxyribonuclease, and amiloride, life expectancy is approximately 50% at 30 years.² Once bronchopulmonary infection is established, most patients with CF will die of severe bronchiectasis caused by inspissated pulmonary secretions.

Hepatic multilobar cirrhosis occurs in 5% to 15% of patients with CF,³ with onset in the first decade of life, and progresses to portal hypertension, hypersplenism, and variceal bleeding.⁴ For those patients liver transplantation is the only effective treatment option to improve length of survival and quality of life. To date, the presence of associated significant lung destruction has prevented many teams from embarking on liver transplantation because only combined replacement of irreversibly damaged lung and liver could offer hope of prolonged survival.

In this study we have analyzed our results with combined lung and liver transplantation in patients who had CF combined with end-stage lung and liver disease.

Patients and methods

Between April 1989 and March 1995, 25 patients with CF were referred and accepted for lung and liver transplantation in Broussais Hospital. The condition of the patients was assessed by physicians experienced in the treatment of patients with CF, and a consensus was reached by the CF French Transplant group regarding the suitability and acceptance of candidates. Patients were selected for associated procedures (i.e., heart-lung-liver or double lung-liver transplantation) on the basis of a deteriorating clinical status indicating a limited life expectancy. Evidence of critically ill condition was suggested by (1) more frequent hospitalizations for pulmonary infection and loss of functional lung capacity, (2) complications of portal hypertension such as variceal hemorrhage, (3) emaciation despite parenteral feeding, (4) necessity for nasal intermittent positive-pressure ventilation for severe hypoxemia and hypercapnia used for sudden deteriorations and as a bridge to lung transplantation,⁵ and (5) life-threatening pulmonary and liver complications such as pneumothorax, hemoptysis, or severe gastrointestinal bleeding.

All patients accepted for the combined procedure had severely compromised pulmonary function. The mean forced vital capacity was 34% and the mean forced expiratory volume in 1 second was 29% of predicted values. All patients were hypoxic, requiring supplemental

oxygen. All had end-stage liver disease with severe cirrhosis and portal hypertension, and all had esophageal varices as seen with an endoscope. One patient had hepatopulmonary syndrome with severe hypoxemia and an intrapulmonary shunt of 35% despite good results of pulmonary function tests. The clinical status of all patients is outlined in Table I. Sputum cultures before transplantation grew mainly *Pseudomonas* species (Table II).

Prospective candidates were evaluated to identify relative contraindications to transplantation, which included poor nutritional status and renal dysfunction. Controlled diabetes mellitus, previous thoracic surgery (lobectomy, pleurodesis), and colonization of sinuses or respiratory passages are no longer considered to be contraindications. Because waiting periods for transplantation can be protracted and the condition of the patients often deteriorates during this time, all patients in this group participated in a preoperative program of pulmonary rehabilitation, with regular intensive physiotherapy. Noninvasive mechanical ventilation was instituted if required in deteriorating situations of severe hypoxemia and hypercapnia. Patients with inadequate nutritional status benefited from parenteral nutrition or jejunostomy feeding. In cases of chronically infected paranasal sinuses, bilateral antral washouts or antrostomies were performed.⁶ At the beginning of our experience when heart-lung transplantations were being performed, recipients were all evaluated and accepted for domino procedures.

Donor organs and procurement. Donors were selected on the basis of standard criteria for separate heart-lung or lung transplantation and liver transplantation. The following factors were particularly important: good pulmonary function as determined by an arterial oxygen tension of 150 mm Hg or greater at an inspired oxygen concentration of 40%, adequate size matching, chest roentgenogram showing no abnormalities, viral studies negative for human immunodeficiency virus (human T-cell lymphotropic virus types I and II) and hepatitis B and C, ABO compatibility, no history of lung disease, negative sputum Gram stain results, and short periods of mechanical ventilation. Only persons who smoked heavily were not accepted as donors. Unless transplantation was urgent, cytomegalovirus mismatching was not accepted for a recipient negative for cytomegalovirus. For the liver to be accepted, normal liver function test results were required.

Donor operation. In each case, all organs were obtained from a single donor by means of standard harvesting techniques. Before retrieval of the heart and lungs, all donors were given heparin intravenously (250 U/kg) and a bolus of intravenous methylprednisolone (1 gm). Prostaglandin E₁ (1000 µg) was administered directly and rapidly into the pulmonary artery. Cold Papworth solution (20 mg/kg) was then infused into the pulmonary artery with simultaneous infusion of crystalloid cardioplegic solution into the ascending aorta for heart and lung preservation.⁷ The liver graft was cooled and preserved with University of Wisconsin solution as described elsewhere.⁸

Recipient operation. The combined but separate procedures of thoracic and abdominal organ transplantation were performed in the same operative sitting. All operations, including the three cases of sequential double lung transplantation, were performed with the use of cardio-

pulmonary bypass because of the critical nature of the recipient's condition. We proceeded with liver transplantation after completion of the lung implantation, termination of bypass, and reversal of heparinization. The sternotomy remained open as the liver transplantation was done to allow access for temporary portoatrial shunting. This was needed in two patients. The sternotomy and chest wound were closed before the biliary anastomosis was fashioned to minimize the risk of contamination.

We performed heart-lung transplantation in the first five patients with a full-sized liver in four and a partial liver in one patient to achieve proper size matching. As the technique of lung transplantation evolved, we performed a bilateral en bloc technique in one patient with direct revascularization of bronchial arteries.⁹ This procedure was complex, and the next three patients had bilateral sequential double lung implantations in combination with liver transplantation. Most recently, for a major size discrepancy between the donor and recipient, we performed a bilateral sequential lobar transplantation from a split left lung associated with a reduced liver lobe transplantation. From a left lung bipartition, the upper lobe was implanted into the right side of the thorax and the lower lobe into the left pleural cavity.¹⁰ This patient received a partial liver (left lobe). Another patient with a large thorax but a small abdominal cavity underwent a standard heart-lung procedure and received a partial liver (left lobe). Techniques of partial liver transplantation have been described elsewhere.¹¹

Median sternotomy was used for heart-lung and double lung en bloc techniques. An anterior bilateral thoracotomy via the fourth or fifth intercostal space was used for sequential double lung transplantation.¹² During the removal of the infected lung, care was taken to minimize pleural contamination. The bronchus of the native lung was stapled distal to the line of division, and open proximal bronchi were suctioned with disposable devices. The donor bronchus was divided as close to the hilum as possible.¹³ The pleurae were irrigated with povidone-iodine solution after explantation of the recipient's lung. A telescoping technique of anastomosis was used for the tracheal anastomosis. Bronchial anastomoses were performed by an end-to-end technique with a continuous running suture without omentopexy and without telescoping of the bronchi.

Liver transplantation was straightforward in seven patients. In three patients who had had previous abdominal operations, two portosystemic shunts and one laparotomy exploration for meconium ileus, the operation was technically more difficult and intraoperative blood loss was increased. So that ischemic time could be minimized, preliminary preparation of the liver was done during implantation of the lungs. This was particularly useful in the two patients who received a reduced-size liver. Biliary reconstruction was by choledochocholedochostomy with a T-tube in two patients or Roux-en-Y choledochojejunostomy in eight patients.

Postoperative management

Immunosuppression. Postoperative immunosuppression was based on our standard triple-drug therapy for isolated lung transplantation—azathioprine, 2 to 3 mg/kg, together with three doses of equine antithymocyte globulin and

Table I. Patient clinical status

Status	No. of patients
End-stage respiratory failure (FEV ₁ = 29%; FVC = 34%)	
Dependent on supplementary oxygen	10
History of hemoptysis/pneumothorax	5
Hepatopulmonary syndrome	1
End-stage liver failure	
Cirrhosis and portal hypertension	10
Hepatic failure	3
History of variceal bleeding	6
Previous portosystemic shunts	2

FEV₁, Forced expiratory volume in 1 second; FVC, forced vital capacity.

Table II. Infection status before transplantation

Organism	No. of patients
<i>Pseudomonas aeruginosa</i>	9
<i>Pseudomonas cepacia</i>	2
<i>Pseudomonas maltophilia</i>	1
<i>Staphylococcus aureus</i>	4
<i>Aspergillus</i>	4
<i>Candida</i>	2

methylprednisolone (1 gm at operation and 125 mg three times daily for the first 24 hours). Steroids were then withheld for 8 days and resumed at a dosage of 1 mg/kg per day, tapering to 0.2 mg/kg per day by 6 months. Cyclosporine was given intravenously (1 to 2.5 mg/kg per day) for 8 days (doses being adjusted according to renal function and concentration of cyclosporine in the blood). Oral cyclosporine was then started to maintain a serum level of 150 to 250 mg/ml. Episodes of acute lung rejection were controlled with bolus intravenous doses of methylprednisolone (15 mg/kg for 3 days) for grade I or II rejection.¹⁴ Antithymocyte globulin was added for persistent grade I to II rejection or for grade III rejection. Rejection was diagnosed on clinical grounds in the first postoperative week and thereafter on results of transbronchial biopsy. Postoperative management in the early phase was aimed toward maintenance of optimum hemodynamics with restriction of fluid intake to avoid pulmonary edema and to allow early extubation. Bronchoscopic examination, transbronchial biopsy, and bronchoalveolar lavage were performed routinely and when indicated on clinical grounds. Ultrasonography of the liver with Doppler evaluation of the hepatic artery and portal vein were done daily.

Results

From April 1989 through March 1995, 25 patients with CF were accepted onto the transplant waiting list for combined heart-lung-liver or lung-liver transplantation. Ten patients underwent transplantation: heart-lung transplantation was done in five patients,

Table III. Demographic characteristics of CF recipients

	Children (n = 4)	Adults (n = 6)
Age (yr)	11 (10-12)*	20.8 (17-24)
Weight (kg)	29.5 (23-38)	47.6 (42-55)
Height (cm)	136 (122-154)	166 (154-173)
Gender (M/F)	2/2	3/3

*Values in parentheses are ranges.

Table IV. Perioperative data

Ischemic time (min)	
Heart lung	229 ± 7.5
First lung	125 ± 5.4
Second lung	191 ± 6.3
Liver	620 ± 9.2
Duration of operation (hr)	
Mean	12
Range	10-17
Duration of ventilation (days)	
Mean	1
Range	1-21
ICU stay (days)	
Mean	17
Range	10-60
Hospital stay (days)	
Mean	45
Range	10-90

ICU, Intensive care unit.

double lung in four (one with an en bloc technique and three with sequential bilateral lung transplants), and sequential bilateral lobar transplantation and a reduced liver transplantation in one. Demographic characteristics are depicted in Table III. The average waiting time for transplantation was 9 months (range 2 to 30 months). Nine patients died on the waiting list, and six are currently awaiting a combined transplantation. Length of postoperative follow-up ranged from 9 months to 5 years. In our practice, the duration of waiting has been shorter for patients with CF accepted for isolated lung transplantation than for patients with CF accepted for combined transplantation (6 vs 9 months).

Perioperative outcome. Operative and postoperative data are presented in Table IV. Ischemic times are given for both lungs, the left lung being implanted after the right lung. Ischemic time for the liver ranged from 390 to 780 minutes (mean 620 minutes), which is acceptable for liver grafts preserved with University of Wisconsin solution. Perioperative mortality, as defined by death within the first 90 days after transplantation or before patients

Table V. Mortality

	No. of patients
Early mortality (<3 mo after transplantation)	
Liver graft failure (retransplantation)	1
Lung graft failure (ECMO)	1
Late mortality (>3 mo after transplantation)	
Cerebral hemorrhage	1
Obliterative bronchiolitis (retransplantation)	1

ECMO, Extracorporeal membrane oxygenation.

have been discharged from the hospital, was 20% (two patients). One patient who had primary liver graft failure received a second donor liver on postoperative day 5, was reextubated, but subsequently died of unexplained pulmonary edema. One patient had acute lung graft failure and died despite institution of extracorporeal membrane oxygenation. Causes of early and late deaths are summarized in Table V. Actuarial survival was 70% at 1 year and has remained unchanged at 3 years (Fig. 1).

Postoperative complications are documented in Tables VI and VII. Airway complications occurred in two children—tracheal stenosis in one and bronchial stricture on the right side in the patient with bilateral lobar transplantation. Both were successfully treated with laser or dilation therapy. Airway stenting was not used in any of these patients. Five patients had prolonged thoracic drainage for pleural effusion.

Hepatic complications occurred in five patients. Two patients had ascites. In one the ascites was due to a chyloperitoneum, after laparotomy on postoperative day 30 for ligation of lymphatic ducts around the hepatic pedicle, the patient recovered uneventfully. In two other patients, both with choledochcholedochostomy, a biliary stricture developed 3 weeks and 6 months after the operation. These strictures were successfully managed by conversion to choledochchojunostomy. One patient had an obstruction equivalent to meconium ileus. This was successfully relieved with meglumine diatrizoate (Gastrografin) enemas and acetylcysteine orally.

Three patients have had grand mal seizures after transplantation. In two patients reversible cerebral abnormalities were identified on computed tomographic scanning. One patient had a cerebral hemorrhage in the sixth postoperative month as a result of systemic hypertension and eventually died. All patients who had seizures also had elevated systemic blood pressure. De novo insulin-dependent diabetes mellitus developed in four patients.

Table VI. Surgical complications

Complication	No. of patients
Liver graft failure	1
Required retransplantation	
Ascites (chyloperitoneum)	2
Required laparotomy in 1 patient	
Biliary obstruction (strictures)	2
CDC converted to CDJ	
Bowel obstruction	1
Meconium ileus equivalent	
Lung graft failure	1
Required ECMO	
Tracheal stenosis	1
Laser and dilation	
Bronchial stenosis	1
Dilation	
Prolonged thoracic drainage	5

CDC, Choledochocholedochostomy; CDJ, choledochojejunostomy; ECMO, extracorporeal membrane oxygenation.

Table VII. Medical complications

	No. of patients
Pulmonary infections	35
Acute rejection episodes	
Lung	26
Liver	8
Obliterative bronchiolitis	3
Seizures	3
Toxic cardiomyopathy	1
De novo diabetes mellitus	4

Infection was a significant cause of morbidity despite antibiotic prophylaxis administered to all recipients on the basis of the most recently available Gram stain, culture, and sensitivity of the recipient's upper respiratory tract. Antibiotic prophylaxis was given for 2 weeks and was stopped if no evidence of infection was present. The linearized infection rates were 2.2 episodes per 100 patient-days. There was a high predominance of bronchitis and pneumonia with *Pseudomonas aeruginosa*. Two patients had bronchial infections caused by *Aspergillus fumigatus*. One patient had meningoencephalitis as a result of herpesvirus infection.

Rejection. Rejection episodes were more frequent during the first 3 postoperative months. Lung rejection episodes were four times more common than liver rejection episodes (26 episodes vs eight episodes). Three long-term survivors had no rejection episodes. Acute episodes of lung and liver rejection were not associated in our series. Rejection episodes were not significantly

Fig. 1. Actuarial survival (Kaplan-Meier) of patients with CF having combined lung-liver transplantation.

more common in patients with CF and combined transplantation than in patients with isolated lung transplantation.

Obliterative bronchiolitis. Obliterative bronchiolitis diagnosed according to established criteria developed in three patients.¹⁵ Among two patients who had grade III obliterative bronchiolitis, one underwent retransplantation during the thirty-eighth postoperative month but subsequently died of bleeding; the second patient chose not to be listed for retransplantation and is currently in poor clinical condition. A third patient with grade I-II obliterative bronchiolitis has a normal lifestyle after having been treated with FK 506.

Discussion

Since the first clinical experience with heart-lung transplantation in patients with CF was reported in 1984, encouraging results in heart-lung and lung transplantation in such patients have been published.^{7, 16-18} The combination of hepatic cirrhosis and portal hypertension, which occurs in 5% to 15% of patients, may preclude a successful outcome of lung transplantation and has generally been considered to be an absolute contraindication. In patients with CF, improved management of pulmonary problems has increased life expectancy and allowed time for extrapulmonary complications to develop.¹⁹ Liver disease usually appears in the first decade of life. The early characteristic of hepatic lesions is a focal biliary fibrosis, which is thought to result primarily from the accumulation of abnormally tenacious bile in intrahepatic ducts, impedes bile flow, and causes biliary fibrosis and consequent cirrhosis. This may progress to severe portal hypertension, as occurred in our 10 patients who had splenomegaly at

the time of assessment. The indications of hypersplenism were reflected in white cell counts and platelets and large varices shown at endoscopy.²⁰

Hepatocyte function as estimated by serum albumin, prothrombin time, and transaminase values may be normal or slightly impaired despite advanced multilobular cirrhosis,⁴ and in our series only three patients had hepatic failure.

The combination of end-stage lung and liver disease in these patients is particularly challenging for both surgical therapy and postoperative management. Questions have been raised regarding the suitability of such candidates for transplantation, particularly in the global context of organ shortage.¹⁸ These patients are often in poor nutritional condition related to severe intestinal malabsorption and chronic infection with multiresistant organisms. Their poor clinical status is aggravated by portal hypertension with episodic life-threatening complications such as gastrointestinal bleeding. Ileus may cause abdominal distention and diaphragmatic splinting. All of these problems may impair the results of combined transplantation. Despite these increased preoperative risk factors, our results with an actuarial survival of 70% at 3 years are similar to those reported for isolated lung transplantation in patients with CF, who have a good quality of life.^{18,21} The genetic nature of the disease is such that recurrence in transplanted organs is highly unlikely. This has been demonstrated for lung transplantation²² but not for liver transplantation. Nevertheless, in our first patient with a 5-year follow-up, repeated liver biopsies taken when indicated for suspected rejection episodes have not shown recurrence of the disease. In this report, 50% of the patients accepted for combined transplantation died while awaiting a donor organ, essentially because of an unacceptably protracted waiting time (mean 9 months). The regulations regarding sharing organs should be reconsidered to gain a priority for patients who have combined end-stage lung and liver disease.

The important question, then, is when and which patient with CF and associated lung and liver diseases should be referred and accepted for combined transplantation. Encouraging results have been reported for the treatment of portal hypertension with splenomegaly by isolated liver transplantation in patients with CF.^{23,24} In these reports, patients had mild-to-moderate lung disease and, with a mean forced expiratory volume in 1 second of approximately 70%, would certainly not be candidates for

lung transplantation. Noble-Jamieson and colleagues²⁴ reported an impressive improvement in subjective pulmonary symptoms in five children with CF after isolated liver transplantation, with greatly improved exercise tolerance and even decreased sputum production. Improvement in pulmonary function was also reported by Cox,²⁵ but three patients of a total of 10 died of infective complications, as a result of *Pseudomonas* in two and *Aspergillus* in one. Mieles and associates²³ reported on four children and five adults; two died of operative problems, and pulmonary function remained stable or was improved in the seven survivors. In our series, one patient had mild lung disease but also had a hepatopulmonary syndrome with extensive pulmonary shunting of 35% (as measured with albumin macroaggregates) and severe hypoxemia (oxygen tension of 35 mm Hg).²⁶ Isolated liver transplantation in this syndrome has reversed hypoxemia according to occasional reports,²⁷ but a recent report from our group has shown poor results with increased mortality in patients with hypoxemia (oxygen tension <60 mm Hg).²⁸ Therefore we considered isolated liver transplantation contraindicated for this patient.

Among the various surgical options available for combined transplantation, the two-stage procedure was adopted with completion of the heart-lung or bilateral sequential double lung transplantations before the liver operation was done. This procedure allows time for the liver to be prepared during implantation of intrathoracic organs and thus minimizes hepatic ischemic time. The thorax was left unclosed to facilitate cannulations should there be a need for temporary portoatrial shunting for liver implantations. This was required in two patients and was done with a centrifugal pump without heparinization. Thus dissection and implantation of the liver was performed without anticoagulation. This approach greatly facilitated organization and operative conditions for both teams, which could work in good coordination but separately. Other possible strategies include that of Wallwork, Williams, and Calne,²⁹ who proposed the integrated but staged and sequential procedures with prebypass dissection of the heart and lung and the liver and implantation of the liver with the aid of bypass. As the technique of lung transplantation has evolved,¹² the introduction of the anterior bithoracosternotomy approach for sequential bilateral lung transplantation has meant that the separate implantation of lungs and liver is the only surgical option possible.

Although biliary reconstruction, once considered the Achilles heel of liver transplantation,³⁰ has become standardized, biliary strictures remain a significant source of complications in our patients with CF. Biliary strictures developed in the only two patients who had biliary reconstruction by choledochocholedochostomy; this complication was managed by conversion to a Roux-en-Y choledochojejunostomy. We believe that choledochocholedochostomy should be avoided in patients with CF because the diseased recipient bile duct may play a major role in causing stricture.

Scarcity of suitable donor organs, even more critical in the pediatric population, has prompted surgeons to develop techniques of liver¹¹ and pulmonary reductions. We¹⁰ recently developed a technique of split lung with the use of bilateral lobar transplants from a donor left lung. The technique of combined reduced-liver and bilateral lobar lung transplantation was successfully performed in one child. Lobar transplantation from living related donors has been proposed for isolated lung³¹ or liver transplantation in children.³² Discharged patients had dramatic improvement in pulmonary function as reflected by forced expiratory volume in 1 second and forced vital capacity, with satisfactory blood gases on exertion and improved quality of life despite the morbidity caused by complications. Incidence of lung or liver rejection episodes was comparable with that of isolated repeated organ transplants, and there was no demonstrable immunosuppressive effect of an additional liver allograft from the same donor, as has been reported in clinical³³ and experimental settings.^{34, 35} The incidence of obliterative bronchiolitis was disappointingly high (40%). Response to augmented maintenance immunosuppression was inconsistent, but the condition of two patients was stabilized by converting cyclosporine therapy to FK 506. Retransplantation was performed in an additional patient. Retransplantation remains controversial for obliterative bronchiolitis because of poor reported results and scarcity of donor organs.³⁶

This report shows encouraging results for combined lung and liver transplantation with a morbidity and mortality equaling that of separate replacements. It demonstrates the feasibility and potential of the combined procedure in carefully selected patients with CF who have chronic respiratory failure with advanced cirrhosis and thus minimal life expectancy. Close cooperation of clinicians with

complementary specialist interests is of utmost importance.

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Discussion

Dr. Magdi Yacoub (London, England). Dr. Couetil, your paper raises many issues. I would like to limit myself to three.

The first relates to the therapeutic potential of combined organ transplantation. Previously there was anecdotal evidence from our group and others that combined heart, lung, and liver transplantation or heart and liver transplantation is worthwhile. Your report, however, show fairly definitively that this is a viable approach by providing a detailed analysis of a relatively large number of patients.

The second issue relates to the potential of multiorgan transplantation for inducing specific immune tolerance. We know clinically that transplantation of the lungs with the heart does impart specific immune tolerance to the heart in that acute rejection is rare. Furthermore, our group and others have good evidence that the incidence of accelerated coronary sclerosis in heart-lung transplantation is extremely low, again suggesting a degree of specific immune tolerance induced by the transplanted lung.

Interestingly, the liver has been thought to have almost magical properties in inducing specific immune tolerance, particularly in experimental models. A variety of mechanisms have been thought to be responsible, including transplantation of the hepatocytes themselves or dendritic cells and reticuloendothelial cells or, last, through the secretion of soluble class I major histocompatibility complex antigens. This observation has been validated repeatedly in experimental models, particularly by Sir Roy Calne's group. In the human being, however, this information again remained anecdotal. We thought we had

some evidence that transplantation of the liver, either with the heart or with the heart and lung, does have an effect in imparting specific immune tolerance. Our first patient who had heart, lung, and liver transplantation for CF is alive and well 9 years later with no evidence of either coronary sclerosis or, more important, obliterative bronchiolitis. I would like you to comment on this in view of your statements about the incidence of acute and chronic rejection in these patients.

My final point, a relatively trivial one, concerns technique. We have found that simultaneous heart, lung, and liver transplantation has advantages. While the thoracic surgeon is implanting the heart and lung block, another surgeon can easily be performing liver transplantation. That shortens the operating time. This approach usually is combined with cannulation of the femoral vein, and that can facilitate the anastomosis of the inferior vena cava, either above or below the diaphragm. After discontinuing bypass the inferior vena cava cannula can be left to act as a shunt into the right atrium through the superior vena cava cannula.

Dr. Couetil. Your first question concerned the potential of the donor liver inducing tolerance. We were very disappointed in this respect, because most of our patients had many rejection episodes, particularly in the lungs. Three patients had no rejection episodes of the liver or lungs, but the seven other patients had many rejection

episodes. We are aware that in clinical studies combined transplantation of the kidney and liver offers better results regarding the number and the grade of the rejection episodes. We are also aware that experimental results have shown that when the liver is transplanted with other organs from the same donor, the rate of rejection episodes is lower. But I think that in those series the liver has always been transplanted before the other organs (i.e., the kidney in clinical studies or before the heart in experimental studies. In our series the liver was transplanted after the lungs, and that may be part of the explanation for the lesser organ tolerance. Experimentally, it has been shown that if the liver is transplanted just after the other organs, there is no induction of tolerance.

Your second question concerned the advantage of simultaneous lung and liver transplantation. Perhaps simultaneous transplantation explains why you had fewer rejection episodes in your series than we had with sequential implantation, the lungs first and the liver second. However, in defense of our technique, we implant the lung or the heart and lungs first and we completely discontinue cardiopulmonary bypass. We control hemostasis, and we start the liver transplantation as a separate operation. Cannulation for an eventual portosystemic shunt for the liver transplantation was required in only two patients in our series. In eight patients it was not necessary.

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