Single- and Double-lung Transplantation

Problems and Possible Solutions

S. RAJU, M.D., B. J. HEATH, M.D., E. T. WARREN, M.D., and J. D. HARDY, M.D.

There is a resurgence of interest in single- and double-lung transplantation for end-stage disease. An experience with six double-lung and three single-lung transplants is reported. The lungs were procured from a distance of up to 600 miles and the heart was shared with another team for transplantation in seven of nine instances. The operative mortality rate was 33%. Early transplant infections of donor origin were lethal. Late transplant pneumonitis was well tolerated and recovery was the rule. Three of nine cases had significant tracheal suture line stenosis and were managed conservatively. A technique of bronchial artery implantation using a conduit tailored from donor aorta is described. Transplant rejection was easily diagnosed and treated. Other notable complications included occasional massive pleural fluid loss, temporary space problem, and a delay in the 'resetting' of chemoreceptors resulting in moderate post-transplant hypercarbia accompanied by episodes in which the patient felt hypoxemic despite the maintenance of excellent levels of blood gases. A comprehensive rehabilitation program begun before operation is essential for success.

THE FIRST RECORDED lung transplantation in humans was performed in 1963.[1] Even though many of the technical[2–6] and physiologic[7–15] aspects of the procedure had been clarified in the experimental setting, long-term clinical success was not attained until after the advent of cyclosporine. Enthusiasm for the procedure was rejuvenated by the successful series reported by the Toronto group.[16] Since then an experience with more than 175 cases, the majority of them single-lung transplants, has been accumulated worldwide.[17] Even though survival statistics at this early stage of experience are encouraging, several problems have been identified, the resolution of which may further improve the outlook for this procedure.

Presented at the 101st Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 3–6, 1989.

Address reprint requests to Seshadri Raju, M.D., Department of Surgery, University of Mississippi Medical Center, 2500 North State Street, Jackson, Mississippi 39216-4505.

Accepted for publication January 19, 1990.

From the Department of Surgery, University of Mississippi Medical Center, Jackson, Mississippi

Case Material

In the last 3 years a total of six double- and three single-lung transplantation procedures were carried out at the University of Mississippi Medical Center. The indications are outlined in Table 1.

Technique

Donor Procedure

Two lungs were procured locally and seven others from distances of up to 600 miles. The heart was shared with another transplant team in six instances. Cold ischemia time and details of other organ harvest are detailed in Table 2. The entire cardiopulmonary block was harvested as a unit in two instances and the organs were separated at the back table. In all others the lungs were harvested after excision of the heart by the cardiac team. In either case mobilization of the lung block consisted of digital retropericardial dissection from the diaphragm to the carina level, proceeding anterior to the esophagus. The trachea was identified between the vena cava and the aorta in the upper mediastinum and later clamped and divided at about five rings above the carina. The main pulmonary artery was divided midway between the pulmonary valve ring and the bifurcation. The left atrium was divided midway between the atrioventricular groove and the confluence of pulmonary veins. When cardioplegia solution was used for the cardiac harvest, it was vented through an incision in the left atrial appendage and not through an incision in the pulmonary vein, as is often done. The azygous vein was divided near the right hilum. The ligamentum arteriosum was divided and the left pulmonary artery was mobilized in the mediastinum. With division of the inferior pulmonary ligaments, the entire lung block could

TABLE 1. *Single- and Double-lung Transplants: Patient Data and Indications*

Patient	Sex	Age (yrs)	Indication
Single-lung Transplantation			
W.B.	M	56	Idiopathic pulmonary fibrosis
I.M.	F	49	Idiopathic pulmonary fibrosis
M.F.	M	38	Idiopathic pulmonary fibrosis
Double-lung Transplantation			
K.M.	F	29	Bilateral cystic bronchiectasis and pulmonary fibrosis
J.C.	M	45	COPD
D.W.	F	27	Cystic fibrosis
F.S.	M	60	COPD
R.D.	M	46	Alpha-1 deficiency
H.K.	M	52	COPD

be excised away from the descending aorta and the esophagus by placing gentle traction on the divided trachea from above and the diaphragmatic pericardium from below. Large pericardial flaps were retained[18] with the specimen to avoid disruption of the peribronchial collaterals (Fig. 1). Throughout the harvesting procedure, a deliberate effort was exercised to minimize handling of the lung parenchyma. In the case of single-lung transplantation, the left lung was separated from the right at the back table by dividing the left bronchus near the carina, the left pulmonary artery at the main pulmonary artery bifurcation, and the left atrium at the cuff draining the two left pulmonary veins. Division of the pericardium in the middle completed the separation. During implantation, the left bronchus was trimmed down to two rings above the take off of the left upper lobe bronchus.

Lung preservation was achieved by topical hypothermia by instilling ice-cold Collins' solution into both pleural cavities through large anterior pleural pericardial incisions. The anesthesiologist was asked to switch over to 100% FIO_2 and clamp the endotracheal tube a few minutes before cardiac arrest. This was done to induce bilateral pulmonary atelectasis, which facilitated rapid pulmonary cooling.[16]

TABLE 2. *Single- and Double-lung Transplants: Organ Procurement Data*

Transplant	Procurement Distance (miles)	Cold Ischemia Time	Incidence of Storage Lung Damage
Single Lung			
W.B.	200	4 hr 15 min	No
I.M.	550	3 hr 35 min	Yes-moderate
M.F.	400	4 hr	No
Double Lung			
K.M.	local	3 hr 35 min	No
D.W.	local	2 hr 45 min	Yes-severe
J.C.	600	4 hr 32 min	Yes-mild
F.S.	400	5 hr 35 min	No
H.K.	175	4 hr 10 min	No
R.D.	400	3 hr 30 min	Yes-severe

Preservation method: Static Euro-Collins in ice.
Hearts: Seven of nine donor hearts were shared for transplantation.

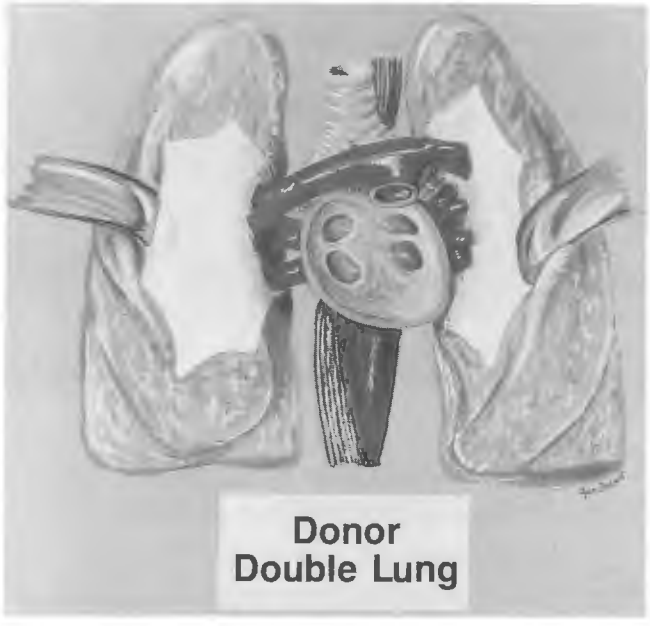
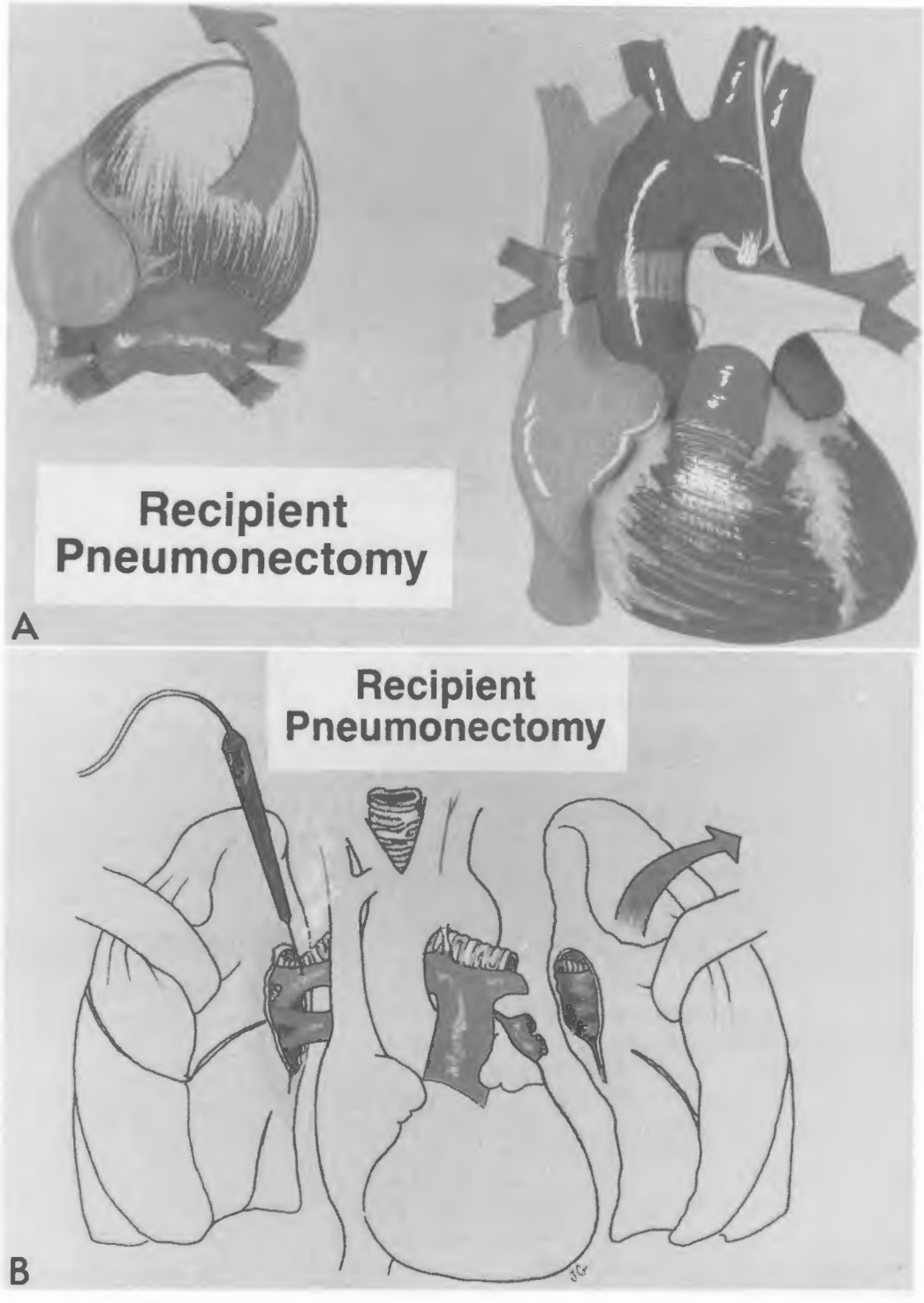


FIG. 1. Donor double lung with retained pleuropericardial flaps and atrial cuff around the pulmonary veins.

Recipient Procedure

Technique of single-lung transplantation.[19] All single-lung transplantations have been performed on the left side, although single right lung transplantation is technically feasible, albeit somewhat more difficult, especially with regard to the atrial anastomosis. Generally the procedure can be performed without heparin and without cardiopulmonary bypass. Partial bypass through the femoral vessels may be required in cases of extreme pulmonary hypertension when unilateral pulmonary vascular clamping is not tolerated by the patient. Through a left thoracotomy, the left lung is mobilized and the left pulmonary artery and veins are divided by stapling instruments as far distally from the hilum as feasible. The left bronchus is also divided near or at the left upper lobe bronchial takeoff. An incision to the left atrium is developed between and including the remaining stumps of the two divided pulmonary veins. The donor atrial cuff is sewn to this incision with running 4-0 Prolene sutures (Ethicon Inc., Somerville, NJ). End-to-end anastomosis of the donor and recipient pulmonary arteries is carried out after completing the bronchial anastomosis with running Prolene sutures. Airway control is obtained during bronchial anastomosis either by introduction of a bronchial blocker or a double-lumen endotracheal tube. Vascular clamps are not released until the left lung is ready



FIGS. 2A–C. Steps in recipient pneumonectomy: (A) division of pericardial veins behind the heart; resection of pulmonary artery retaining part adjacent to ligamentum and recurrent laryngeal nerve. (B) Hilar transection and pneumonectomy. (C) Extraction of tracheal remnant through {R} hilum.

to be ventilated to minimize shunting. The bronchial anastomosis is wrapped with an omental pedicle developed through a small upper abdominal incision and brought up to the left lung hilum behind the xiphisternum.

Technique of double-lung transplantation (Fig. 2). The technique is modified[20] from the one described by Patterson et al.[18] The procedure is carried out under total cardiopulmonary bypass and moderate hypothermia (25 to 28°C) without cardioplegia. Separate vena caval cannulae with snares are used. After bypass is instituted, the pericardial sheaths around the pulmonary veins retrocardially are dissected out and the veins individually divided between staple lines. The right and left pulmonary arteries are divided in the mediastinum near the bifurcation. The

FIG. 2. (*Continued*)

right side of the heart should be vented at this stage by loosening one or both vena caval snares and, if necessary, by introducing a sucker into the right ventricle through an incision in the main pulmonary artery at the site of the proposed anastomosis. Both lung hila can be excised at this point with electrocautery after mobilization of the lung parenchyma with meticulous coagulation division of any adhesions present. The trachea is identified between the vena cava and the ascending aorta and divided close to the carina without disturbing the adjacent vagi. The distal tracheal remnant in the mediastinum is best extracted through the right hilum by traction and electrocautery. Most of the right pulmonary arterial remnant in the mediastinum may have to be extracted to make room for the donor hilum. The left pulmonary arterial remnant is retained to avoid injury to the recurrent laryngeal nerve. It may be necessary to incise the pleuropericardium around the hilum further to make room for the donor lung. These incisions are well away from the phrenic nerve, which should be carefully protected. The donor lung is positioned retrocardially in the orthotopic position. The anastomoses between donor and recipient structures with appropriately sized continuous Prolene sutures are carried out in the following order: trachea, left atrium, and pulmonary artery. The tracheal anastomosis should be wrapped in omentum as previously described (Fig. 3). It has generally been possible to maintain cardiac rhythm throughout and defibrillation has not been necessary. Contractile activity has been relatively muted and has not interfered with satisfactory anastomoses. Left atrial vents have been used routinely to obtain a dry field during the atrial anastomosis. Meticulous evacuation of air is accomplished in the usual manner before onset of left ventricular ejection.

Postoperative Care

Immunosuppression is induced with rabbit anti-human anti-thymocyte globulin (ATG) (2 mg/kg/day) and converted to cyclosporine around the 7th postoperative day, with an overlap of 3 to 4 days until satisfactory cyclosporine blood levels are achieved (whole blood trough level of approximately 800 ng). Imuran (1.5mg/kg; Burroughs Wellcome, Triangle Park, NC) is started on the first postoperative day and dosage is adjusted downward if necessary to maintain a white blood count of more than 5000/mm^3. Oral prednisone at approximately 0.15 mg/kg (10 mg adult dose) is started 3 weeks after operation and gradually reduced to 7.5 mg 3 months after surgery. Rejection episodes are mild as a rule and treated by daily Solu-Medrol boluses (The Upjohn Co., Kalamazoo, MI) (250 to 500 mg/day × 3 days). Patients undergoing lung transplantation face a multitude of hemodynamic, respiratory, metabolic, infectious, immunologic, and other complications.[19,20] A high level of intensive care is necessary for the first few weeks and sometimes much longer if success is to be achieved. Protocols for surveillance and monitoring of patients undergoing a complex cardiopulmonary procedure and transplantation should be in place. After the critical postoperative period, these patients do surprisingly well in the long term, with levels of energy and activity very similar to those of the general population.

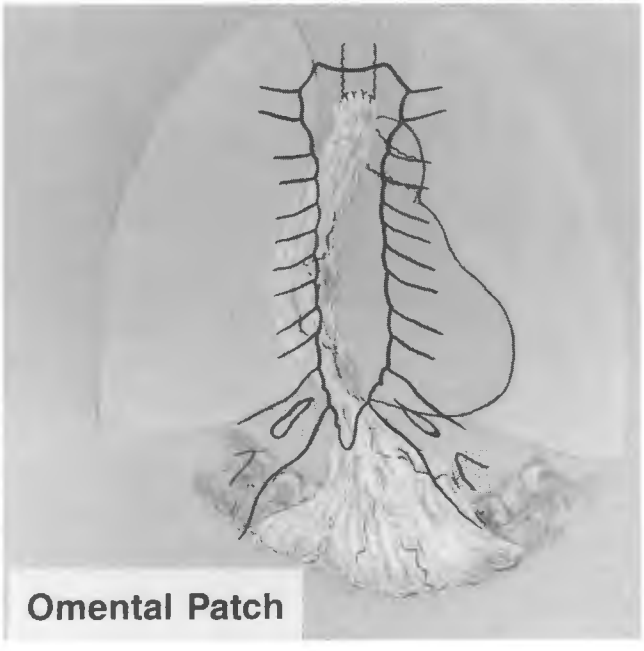


FIG. 3. Omental wrap around tracheal suture line.

TABLE 3. *Single- and Double-lung Transplants: Transplant Infections**

Patient	Onset After Operation	Organism	Outcome
Donor-transmitted Infections†			
D.W.	9 days	Pseudomonas dry and mucoid in sputum and blood	Death from lung abscess and empyema
R.D.	7 days	Candida in blood and body secretions	Death with disseminated candida sepsis
H.K.	7 days	CMV	Death from severe CMV pneumonia
Transplant Infections—Nondonor Origin			
K.M.	2-1/2 mo	Klebsiella in sputum	Recovered
	7 mo	Hemophilus and Streptococcus in sputum	Recovered
	18 mo	Pseudomonas in sputum and blood	Recovered
J.C.	22 days	Proteus in sputum	Recovered
	2 mo 20 days	Proteus and Klebsiella in sputum	Recovered
I.M.	1 mo	*S. aureus* in sputum and blood	Recovered
F.S.	1 mo	*S. aureus* and Enterobacter in sputum and blood	Recovered

* X-ray infiltrate with systemic signs.

† Organism cultured from donor trachea and subsequently from the recipient.

Operative Mortality and Survival

There was an operative mortality rate (less than 30 days) of 33% (3 patients: 2 deaths from donor-transmitted infections and 1 death from pulmonary embolus). An additional patient died at 2 months and 5 days from donor-transmitted infection. Of the five patients discharged from the hospital, three are doing well at 1 year 4 months, 1 year 7 months, and 2 years 5 months, respectively, after transplantation. Two others have since died at 4 months (unexpectedly from an anesthetic complication during transbronchial dilatation of a tracheal stenosis) and 1 year (fungus ball and sepsis in the nontransplanted lung), respectively.

Special Problems

Postoperative Infections

Lung transplant recipients are subjected to donor-transmitted infections in the early postoperative period and later from nondonor sources. Seven of nine transplants experienced significant transplant infection from a variety of infective agents (Table 3).

Case 1

A 27-year-old woman with end-stage lung disease from cystic fibrosis underwent double-lung transplantation. Gram stain from donor tracheal secretions at the time of harvest revealed white blood cells but no organisms. However, 24 hours later, cultures grew dry and mucoid *Pseudomonas aeruginosa*. The patient was immediately placed on appropriate antibiotics. On the ninth postoperative day there was severe respiratory deterioration with production of large quantities of bloody sputum. Cultures grew donor organisms, *i.e.*, dry and mucoid-producing *Pseudomonas aeruginosa*. Despite aggressive antibiotic therapy, both by air aerosolization and systemically, the patient experienced a downhill course and died on the 65th postoperative day. Postmortem examination revealed cavitary destruction of the transplant with empyema by the offending organism.

Case 2

A 29-year-old woman received double-lung transplantation in July 1987 for end-stage lung disease caused by repetitive infective bronchitis starting in childhood. Postoperative course was smooth and the patient was discharged on the 17th day after surgery. She was readmitted on three separate occasions at 2.5 months, 7 months, and 18 months, respectively, after surgery with dyspnea, fever, and sputum production. Transplant pneumonitis was diagnosed based on sputum isolates of *Klebsiella pneumoniae*, Hemophilus, and Pseudomonas on the three admissions, respectively. The patient responded to specific antibiotic therapy on each occasion, with rapid improvement in blood gases, and was discharged after a few days hospitalization in each instance. Currently she maintains excellent lung function and exercise tolerance 2 years and 5 months after operation.

Comments

Donor-transmitted infections are associated with a high mortality rate while later infections of nondonor source appear to be well tolerated by the transplant recipient. Donor-transmitted infections can be minimized by careful choice of donor material. Organs from donors who have

been intubated for more than 72 hours should be rejected. Donor bronchoscopy should be done routinely and lungs with signs of erythematous bronchitis and/or purulent secretions should be rejected. The recipient should be treated expectantly with appropriate antibiotics initially based on donor sputum gram stain findings and later by actual cultures. Candidiasis in the donor warrants low-dose amphotericin treatment of the recipient. We are beginning routine administration of hyperimmune globulin (0.25 g/kg) before operation and at 2-week intervals for 4 to 6 weeks. Specific anti-cytomeglic virus (CMV) hyperimmune globulin is being evaluated under experimental protocol in some institutions. One death in our series occurred from disseminated CMV infection. Among the many factors that predispose to CMV infection are transplantation of lung from a CMV-positive donor to a CMV-negative recipient, administration of polyclonal or monoclonal ATG, heavy steroid dosage for combating rejection, and a debilitated state of the patient. There is general agreement that CMV-negative recipients should not receive organs from CMV-positive donors. There is conscious effort to minimize the use of antithymocyte globulin, especially OKT3. Prophylactic administration of acyclovir or gancyclovir may be considered when extended use of ATG or large steroid boluses is unavoidable. Even when the recipient is CMV positive, reactivation of disease can occur and a high index of suspicion is necessary for proper diagnosis. Periodic CMV titer determination should be carried out and secretions assayed for CMV antigen in symptomatic patients. A temporary reduction in immunosuppression is usually necessary to minimize mortality in affected patients. Sputum is monitored periodically for pathogens, but treatment is not instituted after the tracheal or bronchial suture line has healed unless there is evidence of invasive infection. Some centers routinely use Bactrim (Roche Laboratories, Nutley, NJ) on a chronic basis in immunosuppressed patients as a prophylaxis against Pneumocystis.[16] We have not found this necessary in our lung and other transplant patients because Pneumocystis incidence has been low (less than 1%) with low-dosage steroid administration.

Preservation-related Injury

The absence of a reliable preservation technique that will extend shelf life of the donor lung beyond 4 to 5 hours is among the more serious impediments to lung transplantation. While we and the Toronto group have used the much simpler topical hypothermia technique, others have resorted to infusion preservation with Euro-Collins solution (Fresenius AG, Bad Homburg, West Germany) preceded by prostaglandin administration.[21] It is our impression that there is no dramatic difference between the two techniques in terms of preservation time or quality. In our own experience, the manifestation of severe preservation injury has been unpredictable and does not correlate with cold ischemia time (Table 2). Undoubtedly other donor factors immediately before harvest play a role in the manifestation of preservation injury. Significant storage injury is usually evident within 48 hours after transplantation and is manifested by deteriorating blood gases and increasing parenchymal fluid collection on serial X-rays. Patients are treated by fluid restriction, diuresis, and adequate PEEP to maintain oxygenation. With omental wrap around the tracheobronchial anastomosis,[16,18] even high levels of PEEP are surprisingly well tolerated for prolonged periods of time.

Case 3

A 49-year-old woman received single-lung transplantation for idiopathic pulmonary fibrosis. After operation severe preservation injury manifested by pulmonary edema, deteriorating blood gases, and opacification of the transplant lung on chest X-ray occurred as early as 6 hours after transplantation. The manifestations became worse in the ensuing several days, requiring aggressive therapy with PEEP of up to 20 mmHg, with the patient being paralysis-maintained on a Norcuron drip (Organon Pharmaceuticals, West Orange, NJ). The patient experienced rhabdomyolysis (probably induced by Norcuron) requiring tracheostomy and ventilator support for 3 months, at which time muscle recovery was complete and the patient was weaned from the respirator. During much of this interval, there was bronchiopleural fistula with considerable air leakage through the chest tubes. However, with cessation of PEEP and removal of ventilator support, air leakage stopped and chest tubes were removed without incident. Now 19 months after operation, the patient maintains a clear transplant on chest x-ray, with an arterial PO_2 of 80 mmHg on room air. Her exercise tolerance is good and she maintains a normally active lifestyle.

Comments

Experience with the above case illustrates that even severe storage injury is completely reversible with time. A major reduction in preservation-related injury awaits the development of better storage techniques. In the interim the problem may be minimized by careful choice of donors and by reducing the cold ischemia time as much as feasible. Donors with less than optimal blood gases (less than 400 mmHg on 1.0 FIO_2 at 5 cm PEEP) should be rejected. Infiltrates or other radiographic abnormalities in the potential donor lung are also cause for rejection. Significant smoking history or other points in the history that would suggest a less-than-optimal lung are negative factors in choice of a suitable donor. More recently we have selectively used fructose diphosphate[22] and PGE1 administration in treating overt preservation injury. Placement of a left atrial catheter at the time of surgery may allow more aggressive administration of PGE1 into the pulmonary circulation with simultaneous epinephrine administration into the left atrium to maintain systemic pressure. The pulmonary artery pressure and left atrial pressure should be kept as low as possible, and the oncotic pressure maintained by administration of fresh frozen plasma and other colloids.

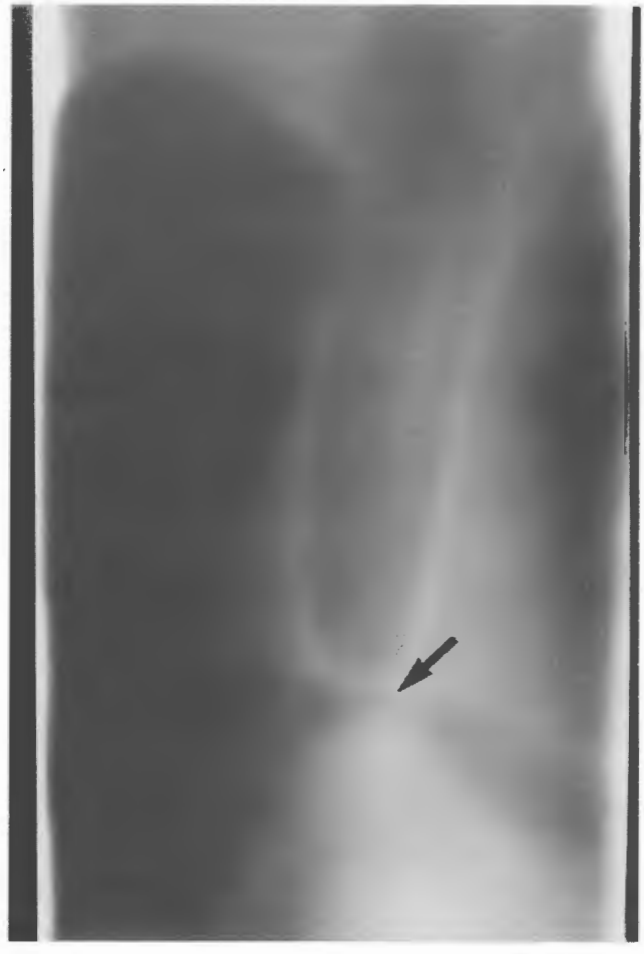


FIG. 4. Severe tracheal stenosis in a patient 4 months after double-lung transplantation.

Transplantation Complications

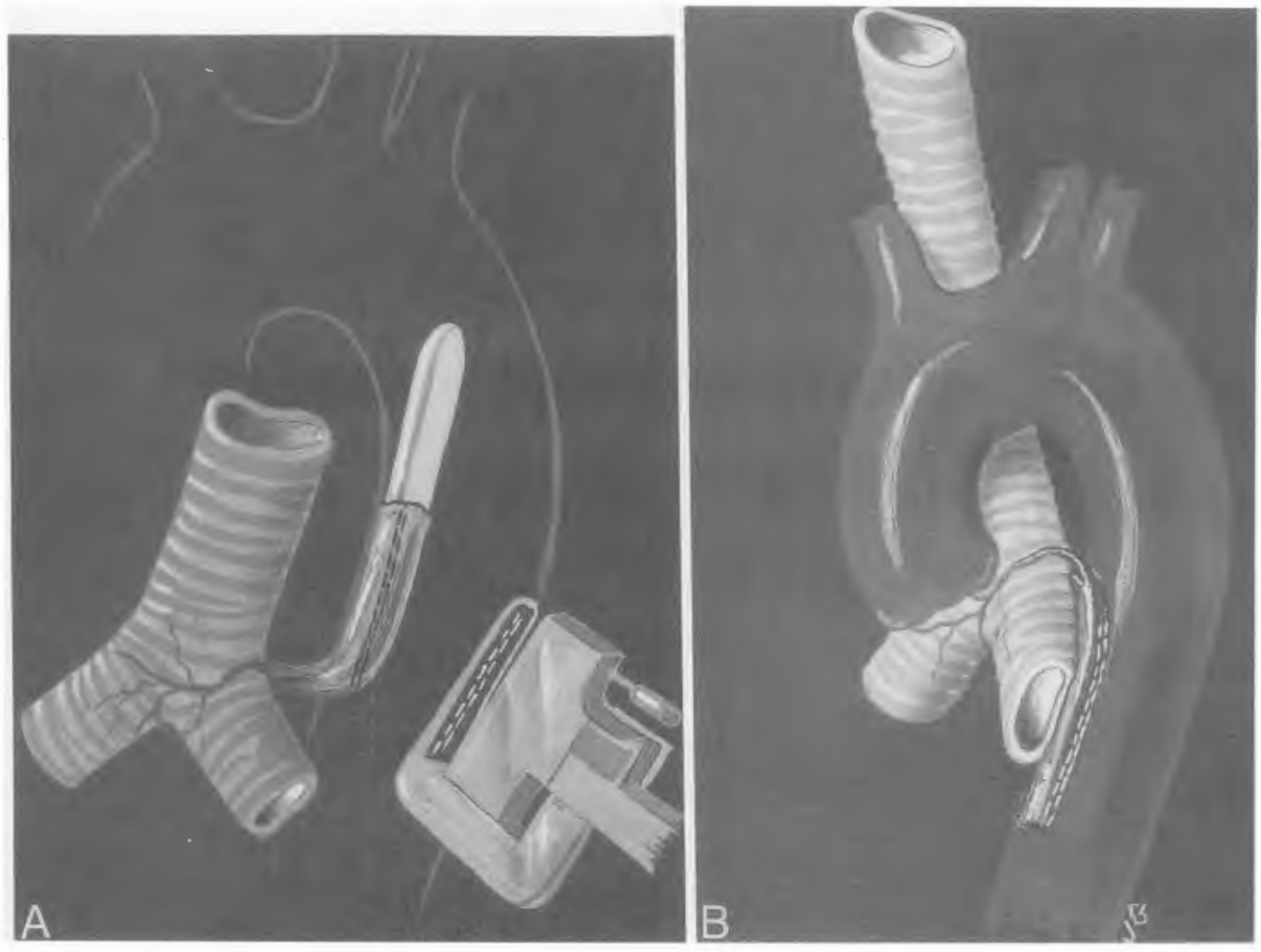
Tracheobronchial Suture Line Problems

With the routine use of omental wrap around the tracheobronchial anastomosis, we have not experienced serious suture line problems in the early postoperative period. However three patients developed significant late tracheal stenosis within several months after transplantation. In two of these the stenosis was approximately 50% reduction in luminal diameter and was easily treated by dilatation during bronchoscopy with partial transbronchial resection of the constricting cicatrix. One patient (Fig. 4) who was otherwise doing well died at 4 months from sudden loss of airway as a result of bleeding during transbronchial resection. Such lesions can be successfully treated with transbronchial placement of chronic indwelling silicone stents across the stenosis.[16]

Early tracheal dehiscence can be avoided by meticulous suture technique, use of monofilament sutures, and the omental wrap, which provides early vascularization to the suture line. Peak airway pressures should be kept as low as feasibly consistent with proper oxygenation. Unnecessary peritracheal or bronchial dissection should be avoided both in the donor and recipient to preserve blood supply. Better lung preservation and consequently reduced use of PEEP will enhance bronchial microcirculation in the postoperative period. In constructing the tracheobronchial suture line, excessive inversion, which tends to produce a shelf and later stenosis, should be avoided. Despite these precautions (Fig. 4), late tracheal stenosis can develop, which is presumably ischemic in origin, augmented by rejection episodes that may further compromise an already tenuous microcirculation. A suitable parallel exists in renal transplantation in which the terminal portion of the transplanted ureter with tenuous blood supply is known to undergo stenosis from rejection and vascular compromise.[23] The low incidence of tracheal suture line complications in heart–lung transplantation due to preservation of coronary–bronchial collaterals suggests that the problem may be solved if bronchial arteries can be reimplanted during isolated lung transplantation. While a Carrell patch of aorta around the bronchial artery can be harvested with the lung, reimplantation is seldom possible in double-lung transplantation either because the patch does not reach the descending aorta or access to the posterior mediastinum becomes limited when the major suture lines are in place. A technical modification can resolve this difficulty (Figs. 5 and 6). The lungs are harvested with the distal aortic arch and much of the descending thoracic aorta by dividing this structure between staple lines at the upper and lower portions of the posterior mediastinum. The esophagus is similarly stapled and divided at the diaphragm and at the level of tracheal division. The lung block may now be excised with the attached posterior mediastinal segment of esophagus and aorta. At the back table, the esophagus is carefully excised without injury to the bronchial vessels. The aorta is opened posteriorly and the opening of the bronchial arteries (usually two in number) is identified near the tracheal bifurcation. Using a 3- or 4-mm Haegar dilator as a stent, a stapling device can be used to construct an appropriate-sized conduit from the aorta feeding into the bronchial arteries. It is more suitable to construct such a conduit from the upper thoracic aorta in double-lung transplantation and from the distal descending thoracic aorta in single-lung transplantation. When the major suture lines of double-lung transplantation are completed, the conduit can be anastomosed easily to the ascending aorta, similar to a saphenous–coronary artery bypass graft. In single-lung transplantation, the conduit is easily anastomosed to the descending thoracic aorta. We have used this concept in two recent patients, but the long-term value of this technique, if any, remains to be assessed.

Transplant Rejection

Almost all transplant patients undergo at least two or more rejection episodes in the first 2 months after transplantation. Rejection episodes are rare before 4 days or



FIGS. 5A and B. Construction of conduit from (A) upper thoracic aorta (for double-lung transplant) and from (B) {L} lower thoracic aorta (for single-lung transplant) to facilitate bronchial artery revascularization.

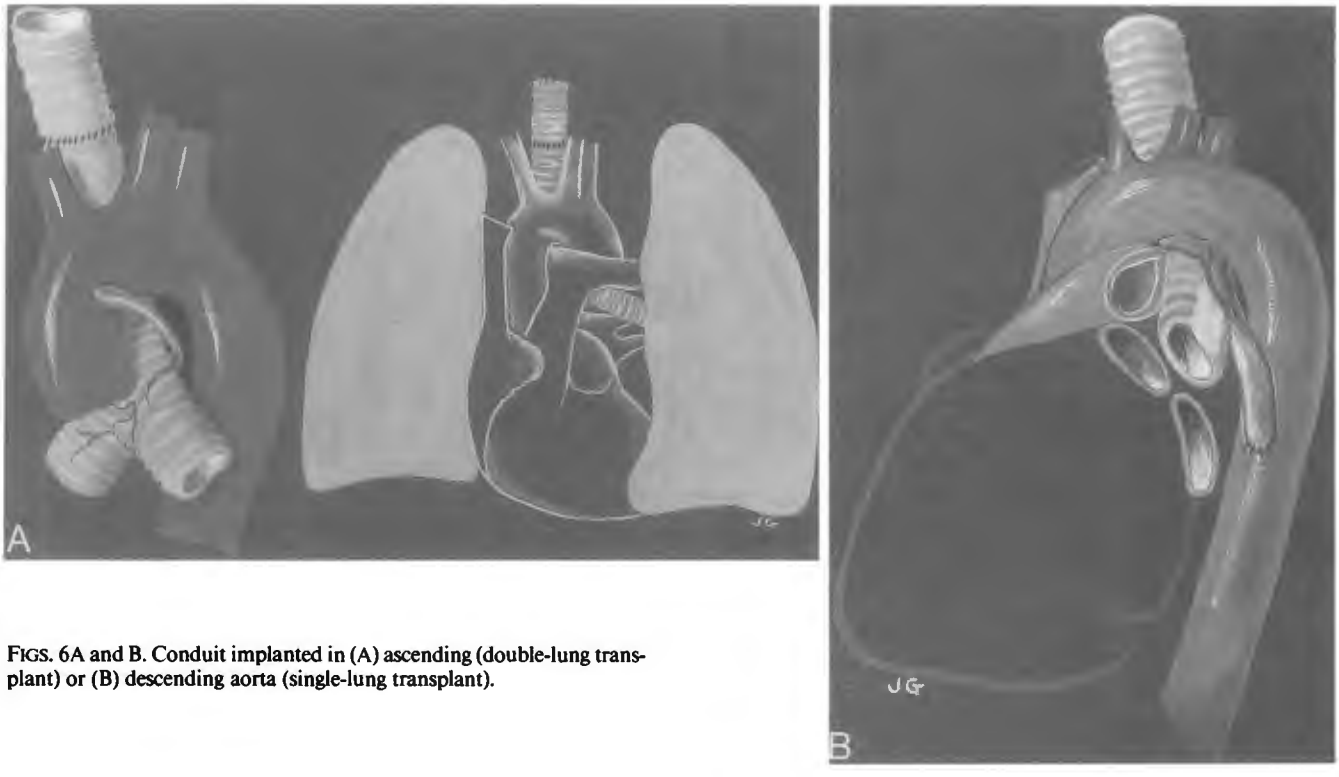
after 3 months. Early rejection at 5 to 7 days will aggravate any existing preservation-related injury and ventilation-perfusion abnormality. Rejection crises respond readily to administration of steroid boluses. Rapid improvement in blood gases is the rule, frequently within 2 to 3 hours after administration of steroids. None of the deaths in our experience were primarily due to rejection. It is our impression that lung transplants can be maintained chronically at an immunosuppression level somewhat less than is required for other organs, such as the heart, the liver, and the kidney. In the cumulative experience of centers performing lung transplantation at present,[17] the incidence of bronchiolitis obliterans appears to be significantly less than is reported for combined heart–lung transplantation.[24] The reason for this marked discrepancy is unclear.

Nutritional and Physical Problems

Patients with long-standing pulmonary disease undergo significant deterioration in nutritional status, muscle mass, and muscle function. An aggressive preoperative program to improve nutrition and muscle function is an integral part of a lung transplant program. Patients who are losing weight should not be considered for transplantation until the weight has stabilized and preferably begun to improve on an appropriate nutritional program. Physical conditioning and exercise tailored to increase strength and endurance enhance the overall condition of the patient before operation and improve his or her outlook to withstand the rigorous postoperative period. Failure to adhere to this aspect of rehabilitation in an early case resulted in a successful transplant in a patient who nevertheless remained an invalid due to his refusal to enter a exercise program after surgery. In this context an appropriate psychologic evaluation before operation is of considerable importance in recipient evaluation.

High-frequency Ventilation

Enthusiasm for high-frequency jet ventilation has waned recently. However it may be useful in select situ-



FIGS. 6A and B. Conduit implanted in (A) ascending (double-lung transplant) or (B) descending aorta (single-lung transplant).

ations of significant transplant dysfunction in which adequate oxygenation by other means is difficult or unavailable. Extracorporeal membrane oxygenation, a theoretical option in similar situations, has not been of practical use in our experience during periods of transplant dysfunction.

Pleural Fluid Loss

Massive loss of fluid through chest tubes from exudation into the pleural cavity is sometimes encountered in the early postoperative period. This may be related to division of lymphatics at the lung hilum or to inability of recipient lymphatics to absorb the exudate (due to sclerosis from repeated previous infections or disruption during the surgical procedure). Other factors, such as excessive exudation from the lung surface as a result of preservation-related injury, may play a part. In one patient fluid loss due to this cause rose to 600 mL per hour and lasted several days after transplantation. Adequate fluid and colloid replacement is necessary under these circumstances.

Space Mismatch

We have generally tried to match the donor and recipient chest sizes based on longitudinal and transverse chest measurements from radiographs. Height, weight, and sex of the patient are also accounted for in donor/recipient matching. More than a 15% discrepancy in chest measurements (length between 1st to 10th vertebra, and transverse chest diameter at 10th vertebra) has been a cause for concern. In situations in which this rule was violated (usually because the emphysematous recipient had a large chest cavity), the temporary space problem evident in early postoperative chest X-rays rapidly disappeared in the ensuing days. Others[16] have reported the opposite situation in which a lung larger than the patient's chest cavity was placed successfully as the diaphragm and the mediastinum moved to accommodate the increased lung mass of the transplant.

Psychological Problems

Patients undergoing transplantation who have been on the verge of death before undergo a series of mood changes after operation ranging from elation to depression and anxiety, and exhibit other frankly abnormal psychological behavior. Most of these resolve with time.

Resetting of Chemoreceptors

With the replacement of the diseased lung by the transplanted lung, resetting of the receptors that control oxygenation, pH, and carbon dioxide tension appears to take several weeks. Most patients have experienced mild to moderate hypercarbia for the first several weeks after transplantation that gradually normalizes later. Either because of inadequate feedback signals from respiratory muscles due to the reduced respiratory effort required after

transplantation or because there is delay in resetting the central chemoreceptors, patients frequently experience a sense of hypoxia in the postoperative period and will often respond by hyperventilation. Repeated blood gas determinations during these episodes are frequently in the normal range and have not shown hypoxemia. These distortions in respiratory mechanisms subside gradually with the passage of time.

Discussion

The diagnosis of lung rejection in our experience has been relatively easy with systemic signs of malaise, fever, and slightly elevated white cell count similar to that seen in other organ transplants. Significant and rapid deterioration in the arterial blood gases with X-ray infiltrates visible a day or so later in the perihilar region completes the 'classic' picture of rejection. Variations are common. When suspected, an initial bolus of 250 to 500 mg steroids should be administered intravenously. Significant improvement in blood gases (often more than 25 mmHg) within 2 to 3 hours after such administration is a strong presumptive evidence for rejection. Other groups[21] have used aggressive transbronchial biopsy to distinguish rejection from infection. This appears to be particularly useful in combined heart–lung transplantation in which rejection appears to occur more frequently and much later than we have seen in our lung transplant group. Because the procedure is apparently attended with minimal risk and morbidity, it may have significant diagnostic value in differentiating rejection from infection.

Enough experience has been gathered worldwide[16,17] to establish single-lung transplantation as the procedure of choice for end-stage interstitial pulmonary fibrosis. Such patients rapidly achieve ventilation–perfusion match in the transplanted lung approaching 80% to 90% of total ventilation and perfusion. The largest segment of pulmonary cripples, *i.e.*, emphysema in the western world, before now have been considered as unsuitable for single-lung transplantation. Severe postoperative ventilation–perfusion mismatches were feared in this group. In a limited experience initiated in France and confirmed in a small group of patients in this country,[25] single-lung transplantation appears to be surprisingly well tolerated, with minimal mortality and morbidity. The ventilation-perfusion mismatch is abnormal in the early postoperative period but rapidly improves with about 75% of ventilation and perfusion going to the transplanted lung at 4 months. These are remarkable findings and, if substantiated, will open lung transplantation to a group of patients, especially those older than 60 years, who cannot tolerate double-lung transplantation under cardiopulmonary bypass.

For other conditions, such as cystic fibrosis or infective end-stage lung disease in which bilateral pneumonectomy is necessary to clear infection, a controversy has erupted[26] as to whether heart–lung or double-lung transplantation is the procedure of choice. Considerable experience with heart–lung transplantation has been accumulated worldwide and the procedure has become standardized with a low incidence of tracheal problems. However initial hopes that the status of lung rejection could be monitored by periodic myocardial biopsies have not materialized. It is clear that either organ can and does undergo separate rejection episodes.[21,24] In addition a surprisingly high incidence of bronchiolitis obliterans (approaching 50% in the experience of one center)[21] is being reported with heart–lung transplantation despite the use of heavy immunosuppression. For reasons that are unclear, the incidence appears to be very much lower after lung transplantation. In addition the principle of limiting transplantation to the diseased organ only has considerable appeal in favor of performing double-lung transplantation for purely pulmonary diseases. Also, in a era of acute organ shortage, it appears wasteful to sacrifice a perfectly healthy heart in recipients with disease confined to the lungs for the performance of heart–lung transplantation. The successful use of 'domino' transplantation of the excised recipient heart may mitigate this argument somewhat against the use of combined heart–lung transplantation for primary lung problems. Double-lung transplantation is at a more primitive stage of evolution compared to heart–lung transplantation and further improvements in technique and results are to be expected. The authors anticipate that in the future heart–lung transplantation will be limited to combined cardiopulmonary pathology, such as Eisenmenger's syndrome and end-stage cor pulmonale. The potential scarce supply of heart–lung blocks compared to lung blocks should further propel practice in this direction. Some centers[25] have already attempted single-lung transplantation for pulmonary hypertension and for Eisenmenger's syndrome with concomitant correction of the cardiac defect. Until recently these conditions were thought to be amenable only to heart–lung transplantation. Thus there is an expansion of options in transplantation varying from single-lung, double-lung, or heart–lung combination to treat end-stage cardiopulmonary pathology. Ultimately each technique dictated by the logistics of donor supply and other considerations will find its proper niche in the armamentarium of the transplant surgeon.

References

1. Hardy JD, Webb WR, Dalton ML Jr, Walker GR Jr. Lung homotransplantation in man: report of the initial case. JAMA 1963; 186:1065–1074.
2. Hardy JD, Eraslan S, Dalton ML Jr, et al. Re-implantation and homotransplantation of the lung: laboratory studies and clinical potential. Ann Surg 1963; 157:707–718.
3. Hardy JD, Eraslan S, Dalton ML Jr. Autotransplantation and homotransplantation of the lung: further studies. J Thorac Cardiovas Surg 1963; 46:606–615.
4. Hardy JD. Human Organ Support and Replacement. Springfield, IL: Charles C Thomas, 1971.

5. Hardy JD, Alican F, Eraslan S, et al. Lung transplantation. *In* Dausset J, Hamburger J, Mathe G, eds. Advances in Transplantation. Proceedings of the First International Congress of the Transplantation Society, Paris, June 27–30, 1967. Baltimore: Williams & Wilkins, 1968. pp. 687–691.
6. Alican F, Isin E, Cockrell JV, et al. One-stage allotransplantation of both lungs in the dog. Am Surg 1973; 177:193–198.
7. Eraslan S, Hardy JD. Differential division of hilar tissues: Effect upon lung function in the dog. Dis Chest 1966; 50:449–455.
8. Eraslan S, Hardy JD, Elliott RL. Lung replantation: respiratory reflexes, vagal integrity, and lung function in chronic dogs. J Surg Res 1966; 6:383–388.
9. Webb WR, Unal M, Cook WA, et al. Growth and function of the transplanted lung in puppies. Clin Res 1965; 13:49.
10. Waldhausen JA, Daly WJ, Baez M, Giammona ST. Physiologic changes associated with autotransplantation of the lung. Ann Surg 1967; 165:580–589.
11. Howard HS, Webb WR. Respiratory paralysis following pulmonary denervation. Surg Forum 1958; 8:466–469.
12. Blumenstock DA. Transplantation of the lung. Transplantation 1967; 5(Suppl):917–928.
13. Greenfield LJ, Chernick V, Hobson WA, Brumley GW. Alterations in pulmonary surfactant following compression atelectasis, pulmonary artery ligation, and reimplantation of the lung. Ann Surg 1967; 166:109–117.
14. Veith FJ. Lung transplantation. Surg Clin North Am 1978; 58:357–364.
15. Veith FJ, Sinha SBP, Blumeke S, et al. Nature and evolution of lung allograft rejection with and without immunosuppression. J Thorac Cardiovas Surg 1972; 63:509–520.
16. The Toronto Lung Transplant Group: Experience with single-lung transplantation for pulmonary fibrosis. JAMA 1988; 259:2258–2262.
17. International Lung Transplant Registry. St. Louis, Missouri.
18. Patterson GA, Goldman B, Pearson FG, et al. Technique of successful clinical double-lung transplantation. Ann Thorac Surg 1988; 45: 626–633.
19. Raju S, Coltharp WH, Gerken MV, et al. Successful single lung transplantation. South Med J 1988; 81:931–933.
20. Raju S, Heath BJ, Warren ET, Hardy JD. Lung transplantation in humans, with emphasis on en bloc technique for simultaneous bilateral transplantation without the heart. Transplant Proc 1989; 21:2594–2595.
21. Hutter JA, Despins P, Higenbottam T, et al. Heart-lung transplantation: better use of resources. Am J Med 1988; 85:4–11.
22. Markov A. Hemodynamics and metabolic effects of fructose 1–6 diphosphate in ischemia and shock—experimental and clinical observations. Ann Emerg Med 1986; 15:1470–1477.
23. Bennett AH. Urologic complications of renal transplantation. *In* Cerelli J, ed. Organ Transplantation and Replacement. Philadelphia: JB Lippincott, 1988. pp. 433–438.
24. Burke CM, Theodore J, Baldwin JC, et al. Twenty-eight cases of human heart-lung transplantation. Lancet 1986; i:517–519.
25. Trulock EP, Egan TM, Kouchoukos NT, et al. Single lung transplantation for severe chronic obstructive pulmonary disease. Chest 1989; 96:738–742.
26. Jones K, Higenbottam T, Wallwork J. Successful heart-lung transplantation for cystic fibrosis. Chest 1988; 93:644–645.

Discussion

DR. JOHN C. MCDONALD (Shreveport, Louisiana): It is a pleasure for me to comment on this major presentation. This is the latest of many contributions to transplantation by Dr. Raju, his teacher Dr. Hardy, and their colleagues.

The manuscript is a compendium of the knowledge relative to lung transplantation and the lessons learned from nine patients, which is certainly not a small clinical experience in this field. In fact I believe it to be the largest experience yet reported in the United States.

As you know lung transplantation has lagged behind the development of the transplantation of other extrarenal organs. I wish to address only a few points made in this paper.

The first relates to infection, which historically has been the major obstacle to success of lung transplantation. The patients themselves are usually infested, if not infected, and the donor lung is rarely sterile. The patients in this series are no exceptions and almost all of them suffered some form of infection during their hospital course.

The principal reason cyclosporin has revolutionized extrarenal transplantation lies in its capacity to suppress alloimmune responses while sparing pre-existing immunity and natural host defenses, including phagocytosis. Thus I wish to inquire how this group, as well as the Toronto group, selected the immunosuppressive protocol, which was to use ATG and Imuran from the onset while cyclosporin was added only 4 to 5 days after the transplant procedure.

Theoretically this would appear to be the worst of possible worlds because, teliologically, it seems best to start the cyclosporin and add the more toxic agents after the patient has had time to clear the microbial infestation.

Second, I would like to hear some discussion concerning the predictability of the health of the lung implant.

It appeared to me that you were entirely unable to predict how well the organ would function, no matter what the variation in organ-preservation time.

This problem is a thread that runs throughout the field of transplantation. Clearly it is true in liver and kidney transplantation, in which 10% of liver and kidney transplants go through a period of primary graft nonfunction, which is totally unpredictable in relation to donor characteristics. Dr. Raju, how you are approaching this problem?

Finally, although this comment may be presumptuous on my part and perhaps out of place, I would like to express my admiration of Dr. Raju for his continuing contributions to transplantation. Dr. Raju has worked quietly, reliably, and consistently in this field now for almost 20 years and has proved himself to be one of Dr. Hardy's most brilliant students. We are indebted to him for scholarly work regarding small bowel transplantation, organ preservation, lung transplantation, and many other areas of thoughtful studies in this field.

DR. GEORGE JOHNSON, JR. (Chapel Hill, North Carolina): I reviewed the manuscript with Dr. Frank Veith of New York and Dr. Thomas Egan of Toronto and now of Chapel Hill, both reknown transplant surgeons who are unable to be with us.

There is little doubt that this study represents another major contribution to this field from Mississippi. With Dr. Hardy's pioneering efforts and Dr. Raju's persistence in the laboratory and his clinical efforts, they now have one of the largest series in North America.

The manuscript warrants a few comments. Excision of the lung *in situ* rather than *en bloc* incision of the heart and lung and cold emersion of the lung rather than flushing, as Dr. Raju presented it, although controversial subjects, were thought to be appropriate by my colleagues.

There were some technical questions, however, regarding the manuscript. Do continuous sutures for tracheal anastomosis lead to more postoperative stenosis than would interrupted sutures?

Is performing the left atrial anastomosis without cardioplegia difficult?

Are you concerned about air embolus in this setting and, similar to Dr. McDonald, why don't you introduce cyclosporin therapy immediately because it can be given intravenously?

You have developed an ingenious method to create a vascular conduit in an attempt to establish bronchial artery arterial systemic blood supply. Do you have proof that this stays open?

As a nontransplant surgeon, I think I am on the bank of a mountain stream watching some skilled fishermen haggling over the best lure to use. The real question I would ask: Are there any fish in the stream?

With 175 lung transplants having been done and a 40% long-term survival rate, as reported by Dr. Raju, does this presentation herald the next stage of lung transplantation? Have the pioneering efforts of Dr. Hardy 26 years ago finally matured to where transplantation of the lung