Clinical Investigation

Single-Lung Transplantation for Pulmonary Hypertension
Three-Month Hemodynamic Follow-up

Michael K. Pasque, MD; Elbert P. Trulock, MD; Larry R. Kaiser, MD; and Joel D. Cooper, MD

Background. Shorter waiting times, relative technical simplicity, and satisfactory application to a broad spectrum of patients has made single-lung transplantation an attractive option in the treatment of patients with end-stage pulmonary hypertension.

Methods and Results. Seven patients with pulmonary hypertension underwent single-lung transplantation. Simultaneous closure of associated atrial septal defects was accomplished in two patients. Despite severely compromised pretransplant right ventricular function in all patients, there was no early or late mortality. Right ventricular functional recovery as characterized by hemodynamic assessment before and at a mean of 13 weeks posttransplant was nearly uniform and characterized by a drop in 1) pulmonary arterial systolic pressure from 92±7 mm Hg to 29±6 mm Hg (p=0.001), 2) central venous pressure from 10±6 mm Hg to 1±2 mm Hg (p=0.02), and 3) pulmonary vascular resistance index from 1,924±663 to 232±73 dyne·sec·cm⁻⁵ (p=0.001). Radionuclide ventriculography before and at a mean of 17 weeks posttransplant documented a significant (p=0.006) increase in right ventricular ejection fraction from 22±15% to 51±11%. Quantitative pulmonary perfusion scintigraphy at a mean of 17 weeks posttransplant demonstrated a significant (p=0.001) increase in perfusion to the transplanted lung from 56±6% to 89±7%. There was a concomitant, slight but significant (p=0.004) decrease in ventilation to the transplanted side from 56±6% to 49±8%. After transplantation, all patients returned to New York Heart Association functional class I or II from their preoperative levels of class III or IV.

Conclusions. These early follow-up data cautiously support the option of single-lung transplantation in patients with pulmonary hypertension, although long-term durability of these hemodynamic changes deserves documentation before widespread application. (Circulation 1991;84:2275–2279)

Transplantation in patients with end-stage pulmonary hypertension has previously been limited to en bloc heart-lung transplantation.1–3 Although achieving moderate success, this option has been limited by donor availability, technical problems, and subsequent occurrence of bronchiolitis obliterans.4 In light of the relative technical simplicity of single-lung transplantation, the greater availability of single-lung blocks, and satisfaction with application across a broad spectrum of end-stage lung disease, we undertook application of single-lung transplantation in a complicated subset of patients with pulmonary hypertension. As a fundamental part of this program, a careful prospective evaluation of right ventricular function was undertaken before and at intervals after transplantation. This report describes our experience with our first seven consecutive single-lung transplants for pulmonary hypertension.

Methods

Patient Population

The study population consists of all seven patients with pulmonary hypertension who underwent consecutive evaluation and subsequent single-lung transplantation between November 21, 1989 and July 2, 1990, with follow-up completed in all patients up to February 1, 1991. The presumed diagnosis in all seven patients was primary pulmonary hypertension, although secondary pulmonary hypertension (Eisen-
Menger syndrome) cannot be ruled out in the two patients with atrial septal defects. Six of the seven patients were women. Age range was from 28 to 41 years, with a mean of 34 years.

**Operative Technique**

The technical aspects of single-lung transplantation in patients with pulmonary hypertension have been described previously. Briefly, donor lung retrieval is carried out as we have previously described, with both of the single-lung blocs and the heart being available for use in as many as three separate recipients in as many as three separate institutions. The recipient procedure is carried out through a posterolateral thoracotomy, with standard use of partial cardiopulmonary bypass support during implantation.

All patients undergo routine preoperative left and right heart catheterization (including oximetry) as well as transthoracic echocardiography to rule out the presence of congenital defects or “sprung” patent foramen ovale. Nonetheless, transesophageal echocardiography is routinely used at the time of transplantation as a final check for significant defects and to monitor right ventricular function. Associated atrial septal defects are repaired while on cardiopulmonary bypass before removal and replacement of the recipient lung. Omental wrapping of the bronchial anastomosis and standard immunosuppressive protocols are routinely used. Systemic arterial, pulmonary arterial, pulmonary capillary wedge, and central venous pressures as well as thermodilution cardiac outputs are closely monitored in the postoperative period. Prostaglandin (PGE$_{1}$) may be used postoperatively as a pulmonary vasodilator. Inotropic support is with dobutamine when necessary.

**Statistical Analysis**

Statistical analysis of pretransplant and posttransplant data was carried out with standard paired Student’s t test on a Macintosh IIx using SYSTAT: The System for Statistics. All results are expressed as mean±SD.

**Radionuclide Methodology**

All radionuclide imaging studies were performed according to standard methodology used by the Mallinckrodt Institute of Radiology at Washington University School of Medicine.

Ventilation/perfusion scans were performed by a standard protocol with the use of krypton-81-m gas and technetium-99-m AA (macro aggregate albumin), respectively. Ventilation images were obtained for 200,000 counts in the posterior view, and the imaging time was recorded. The anterior ventilation images were then obtained by using the same imaging time. Posterior perfusion images were obtained for 600,000 counts, and the same imaging time was likewise used to obtain the anterior perfusion images. Anterior and posterior counts were calculated, and the geometric mean of these values was reported.

Radionuclide ventriculography was performed with electrocardiographic gating by using the “pooled” or equilibrium method with technetium-99m-AA-tagged red blood cells.

**Results**

All seven of our patients underwent successful single-lung transplantation. Simultaneous operative closure of known interatrial communications was successfully carried out in two of these patients. All patients survived the operative period and were discharged from the hospital and alive at a mean follow-up period of 47±12 weeks (range, 31–62 weeks).

Donor lung ischemia time averaged 287±55 minutes. The seven patients spent a mean of 10±11 days in the intensive care unit (range, 2–32 days) and a mean of 25±10 days in the hospital postoperatively (range, 15–44 days).

In one patient, severe donor lung dysfunction resulted in profound desaturation and hemodynamic instability in the operating room, requiring over 60 hours on partial extracorporeal membrane oxygenation (ECMO) support via femoral cannulation sites. The patient was subsequently weaned from support and recovered.

Despite marked reversal of right ventricular hemodynamic compromise, most of the patients demonstrated some hemodynamic instability in the perioperative period. This hemodynamic instability was manifested by fluctuations in systemic vascular resistance. The resulting hypotension resulted in the necessity for transient administration of vasodilating agents and may have been contributory to the two postoperative cardiac arrests that occurred in these seven patients. One patient suffered a cardiac arrest on her third postoperative day while undergoing postural drainage therapy on the ward. She was resuscitated and subsequently recovered after a long period of rehabilitation. Another patient suffered cardiac arrest on postoperative day 4 with immediate resuscitation without sequelae. It is our suspicion that both cardiac arrests were associated with episodes of early rejection. These rejection episodes are commonly associated with increased vascular resistance to the transplanted lung, with a resultant stress to the accommodating right ventricle. It is not clear whether the cardiac arrests resulted directly from the suspected rejection. One of these patients had also undergone simultaneous closure of a large ostium secundum defect at the time of single-lung transplantation but it did not appear that this was contributory to the cardiac arrest.

There were no airway complications encountered in this group of patients.

Pretransplantation and posttransplantation hemodynamic data obtained at cardiac catheterization are presented in Table 1. Posttransplantation data
TABLE 1. Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AO systolic</td>
<td>117±15</td>
<td>134±23</td>
<td>0.119</td>
</tr>
<tr>
<td>AO diastolic</td>
<td>75±9</td>
<td>82±15</td>
<td>0.209</td>
</tr>
<tr>
<td>AO mean</td>
<td>90±11</td>
<td>101±20</td>
<td>0.179</td>
</tr>
<tr>
<td>PA systolic</td>
<td>92±18</td>
<td>29±6</td>
<td>0.001</td>
</tr>
<tr>
<td>PA diastolic</td>
<td>41±6</td>
<td>13±8</td>
<td>0.001</td>
</tr>
<tr>
<td>PA mean</td>
<td>64±18</td>
<td>18±5</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart rate</td>
<td>88±16</td>
<td>91±10</td>
<td>0.679</td>
</tr>
<tr>
<td>CVP</td>
<td>10±6</td>
<td>1±2</td>
<td>0.020</td>
</tr>
<tr>
<td>RVEDP</td>
<td>11±9</td>
<td>2±2</td>
<td>0.049</td>
</tr>
<tr>
<td>PCWP</td>
<td>7±2</td>
<td>8±4</td>
<td>0.541</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>2.54±0.98</td>
<td>3.54±0.70</td>
<td>0.065</td>
</tr>
<tr>
<td>SVRI</td>
<td>2,763±766</td>
<td>2,346±759</td>
<td>0.390</td>
</tr>
<tr>
<td>PVRI</td>
<td>1,924±663</td>
<td>233±73</td>
<td>0.001</td>
</tr>
<tr>
<td>SVRI/PVRI</td>
<td>1.52±0.50</td>
<td>10.70±3.70</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Hemodynamic data (n=7) obtained at cardiac catheterization before (mean, 61 weeks; range, 7-241 weeks) and after (mean, 13 weeks; range, 3-30 weeks) single-lung transplantation are displayed as mean±SD. All pressures are in mm Hg, heart rate in beats per minute, cardiac index in l/min/m², and resistance index in dyne·sec·cm⁻⁵. AO, aortic; PA, pulmonary arterial; CVP, central venous pressure; RVEDP, right ventricular end-diastolic pressure; PCWP, pulmonary capillary wedge pressure; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index.

were obtained at a mean of 13 weeks (range, 3–30 weeks) postoperatively. All patients underwent pulmonary ventilation/perfusion scintigraphy (Table 2) and estimation of both right (Figure 1) and left ventricular ejection fraction by radionuclide ventriculography before (mean, 9 weeks pretransplant; range, 1–17 weeks) and at a mean of 17 weeks (range, 10–26 weeks) postoperatively.

Functional status as represented by New York Heart Association functional class markedly improved (p<0.001) after single-lung transplantation from the pretransplant mean of 3.6±0.5 (range, 3–4) to the posttransplant level of 1.3±0.5 (range, 1–2). All patients who were employed or in school (before being disabled by symptoms referable to their pulmonary hypertension) returned to active full-time (40-hour work week) employment or school.

TABLE 2. Pulmonary Ventilation and Perfusion Scintigraphy Data

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Ventilation scan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplanted side</td>
<td>56±6%</td>
<td>49±8%</td>
<td>0.004</td>
</tr>
<tr>
<td>Opposite side</td>
<td>44±6%</td>
<td>51±8%</td>
<td>0.004</td>
</tr>
<tr>
<td>Perfusion scan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplanted side</td>
<td>56±6%</td>
<td>89±7%</td>
<td>0.001</td>
</tr>
<tr>
<td>Opposite side</td>
<td>44±7%</td>
<td>11±7%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Pulmonary ventilation and perfusion scintigraphy data (n=7) obtained before (mean, 9 weeks pretransplant; range, 1–17 weeks) and after (mean, 17 weeks; range, 10–26 weeks) single-lung transplantation. Values are mean±SD.

Discussion

Heart-lung transplantation was developed as a treatment option for patients with severe pulmonary hypertension.1 Success rates have been reasonable, with 1-year survival ranging from 64% to 76%.2-4 Long-term survival has been limited by bronchiolitis obliterans.2-4 More importantly, however, the overall applicability of this procedure to the large subset of patients with primary or secondary pulmonary hypertension has been limited by the availability of suitable heart-lung donors. In addition to the difficulty in finding donors with combined heart and lung function that is reasonable for transplantation, there may be some hesitancy in serving a single recipient with the heart-lung bloc when two or even three recipients can be transplanted when the organs are divided. As a result, waiting times after listing for heart-lung transplantation are often measured in years. Patients with pulmonary hypertension are usually quite compromised by the time they are referred for evaluation and listing for transplantation. This results in a high waiting list mortality rate despite the advances in palliation that have been demonstrated recently.5-10

In light of these facts, single or bilateral lung transplantation for patients with primary pulmonary hypertension or secondary pulmonary hypertension with correctable cardiac defects may be a reasonable transplantation alternative. Recognizing that many questions regarding initial relief of pulmonary hypertension, recurrence of pulmonary hypertensive changes in the transplanted lung, sus-

FIGURE 1. Graphic demonstration of changes in right ventricular ejection fraction measured by radionuclide ventriculography (RVG) after single-lung transplantation (n=7).
ceptibility to short- and long-term rejection, and the early and late recovery of these often severely compromised hearts remained unanswered, we embarked on a prospective application of single-lung transplantation in this subset of patients.

Our early experience clearly defined several distinguishing characteristics of this lung transplantation patient group. First, severely compromised pretransplant cardiac function is the rule. We did not refuse lung transplantation to any patient with pulmonary hypertension on the basis of cardiac function. All of our patients had end-stage right ventricular failure with marked ventricular dilatation, tricuspid regurgitation, a mean right ventricular ejection fraction of 22±15% and a mean central venous pressure of 10±6 mm Hg. In all patients, right ventricular hemodynamic compromise was reversible after single-lung transplantation. The uniform decrease in pulmonary vascular resistance (Table 1) and pulmonary arterial pressure (Figure 2) resulted in improvement of mean right ventricular ejection fraction (Figure 1) to 51±11% and mean central venous pressure (Figure 3) to 1±2 mm Hg at follow-up catheterization.

These hemodynamic results are not unexpected. Similar improvement has been seen in right-sided hemodynamics after administration of medications that chronically lower pulmonary artery pressure and after pulmonary arterial endarterectomy for chronic pulmonary embolism.

Despite these encouraging hemodynamic results, it became readily apparent that the hemodynamic stability was predominantly dependent on the status of the transplanted lung. During episodes of transplant lung dysfunction secondary to variable etiology (postsischemic reperfusion injury, acute rejection, infection, or ventilatory impairment), hemodynamic compromise could be quite pronounced, leading to a need for early postoperative ECMO in one patient and early cardiac arrest in two patients.

Second, significant interatrial shunts exist in a large proportion of these patients. Our early experience suggests that these defects, which range from formal ostium secundum or sinus venosus atrial septal defects to large patent foramen ovales, should be closed at the time of lung transplantation. If not, elevation of right atrial pressures during episodes of transplant lung dysfunction might result in significant systemic arterial desaturation from shunting across these defects. Significant episodic desaturation in two of our initial patients was suspicious for right-to-left shunting across a patent foramen ovale. Although this was never confirmed, concern over this possibility has led us to routinely close all atrial septal defects that are detected by preoperative cardiac catheterization, preoperative transthoracic echocardiography, or intra-operative transesophageal echocardiography. Patent foramen ovales that are believed to be 1 cm in size or greater
or that demonstrate significant shunt by oximetry or echocardiography bubble study are also closed at the time of single-lung transplantation.

Third, the uniformly compromised cardiac status of these patients severely limits their pretransplant preparation. The pulmonary and physical rehabilitation, which is a mandatory part of our routine lung transplant patient preparation, is not possible. Fear of sudden death precipitated by physical exertion is not unwarranted in this group of patients. The resulting poor conditioning may compromise early ventilator weaning and ambulation, which are possible in the majority of our other single and bilateral lung transplant recipients. As a result, longer postoperative ventilatory assistance as well as longer intensive care and hospital stays can be expected.

Fourth, the pulmonary ventilation/perfusion scintigraphy results obtained in these patients postoperatively document a mismatch in the transplanted lung. Perfusion to the transplanted side at a mean of 17 weeks posttransplant markedly increases (Table 2), as expected, from 56±6% (pre) to 89±7% (p=0.001). At the same interval posttransplant, however, the ventilation of the transplanted side decreases (Table 2) from 56±6% (pre) to 49±8% (p=0.004). The cause of this slight decrease in ventilation to the transplanted side is not known. These findings may reflect the mechanical effect of the thoracotomy, a decrease in lung compliance secondary to the increased blood flow to the transplanted side, or other effects of transplantation on the lung. Nonetheless, all of the patients in our series have returned to excellent functional status with improvements in functional class from 3.6±0.5 (pre) to 1.3±0.5 (p<0.001). Their uniform return to work or school after transplantation further documents their lack of functional disability.

Fifth, the question of long-term follow-up, especially regarding the possible occurrence of bronchiolitis obliterans in this patient subset, remains unanswered. There may be a strong predilection to the occurrence of this disease in patients with pulmonary hypertension. Earlier suggestions that single-lung transplantation was not often associated with this process, which has plagued heart-lung transplantation, may have been due to the fact that patients with pulmonary hypertension were not previously represented in the single-lung transplant patient subset. Clearly, the full scope of this problem has yet to be elucidated.

Conclusions

Despite these limitations, we feel that our early experience suggests that single-lung transplantation is a very reasonable alternative to other transplantation options in patients with primary pulmonary hypertension and patients with pulmonary hypertension secondary to selected congenital cardiovascular defects. The long-term durability of the favorable hemodynamic changes documented in this early follow-up is unknown and clearly deserves further investigation before widespread application. This is a difficult patient subset, at best, and application of single-lung transplantation in this manner should be undertaken only in selected centers with a long-term commitment to lung transplantation.

Addendum

At the time of final submission of this article, a total of 12 patients had undergone single lung transplantation for pulmonary hypertension with 11 surviving up to 22 months.

References


KEY WORDS: right ventricular function, primary pulmonary hypertension, secondary pulmonary hypertension, heart-lung transplantation
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M K Pasque, E P Trulock, L R Kaiser and J D Cooper

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