Increased Thromboembolic Events After Lung Transplantation*

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Background: Lung transplantation is a good therapeutic option for end-stage lung disease. Data on thromboembolic complications following lung transplantation are scarce.

Study objectives: To evaluate the incidence of thromboembolic events following lung transplantation, and to determine their possible association with hypercoagulable state.

Design: Retrospective study in a single, tertiary-care, university-affiliated referral center.

Subjects and method: The records of 70 patients who underwent lung transplantation in our institution between September 1997 and September 2003 were reviewed for thromboembolic complications. Parameters pertaining to risk of thrombophilia were measured in the patients with thromboembolic complications.

Results: Thromboembolic complications developed in 6 of the 70 patients (8.6%) at 4 to 24 months after transplantation: deep vein thrombosis (DVT) in 2 patients, pulmonary embolism (PE) in 1 patient, and retinal vein thrombosis in 2 patients. The fibrinogen level was elevated in all six patients, and factor VIII, IX, and/or XI levels were elevated in five patients. Heterozygosity for 5 10-methylene tetrahydrofolate reductase was documented in two patients, and mutation for factor II or factor V-Leiden mutation was found in one patient. Levels of protein C and protein S and activated protein C resistance were within normal range in all patients. Four patients had mildly elevated levels of at least one antiphospholipid antibody; none had a positive lupus anticoagulant test result. Overall, all patients demonstrated abnormalities on hypercoagulability tests.

Conclusions: Thromboembolic complications occur at a high rate (8.6%) in lung transplant recipients and are associated with abnormalities in hypercoagulability. The cause remains unclear. Our results should prompt a high index of suspicion for these potentially fatal complications, which would lead to early diagnosis and successful treatment.

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Key words: antiphospholipid antibodies; deep vein thrombosis; hypercoagulability; lung transplantation; pulmonary embolism

Abbreviations: aCL = anticardiolipin; APC = activated protein C; DVT = deep vein thrombosis; ELISA = enzyme-linked immunosorbent assay; LAC = lupus anticoagulant; MTHFR = 5 10-methylene tetrahydrofolate reductase; PE = pulmonary embolism; RVT = retinal vein thrombosis

In the past 2 decades, lung transplantation has become a good therapeutic option for end-stage pulmonary disease. Survival has improved owing to advances in immunosuppressive therapy, standardization of selection criteria, and improvements in preoperative and postoperative management. Known complications of lung transplantations are acute reperfusion injury, bronchial dehiscence, acute and chronic rejections, and infections; patients are also at increased risk...
of secondary malignancies. Studies have reported that deep vein thrombosis (DVT) and pulmonary embolism (PE) may occur after lung transplantation.¹ ² Nathan et al² found that the incidence of PE after lung transplantation was higher in patients with interstitial pulmonary fibrosis. However, there is a general paucity of data on the association of hypercoagulable state and thromboembolic predisposition in lung transplant recipients. The purpose of this study was to evaluate the incidence of thromboembolic events in lung transplant recipients and the presence of hypercoagulability risk factors in affected patients.

Materials and Methods

We reviewed the records of all patients who underwent lung or heart-lung transplantation in Rabin Medical Center between September 1997 and September 2003 for thromboembolic complications. All the blood test and diagnostic studies were done as part of the routine clinical workup. DVT was diagnosed by duplex study of the legs, PE was diagnosed by CT angiography, and retinal vein thrombosis (RVT) was diagnosed by fundus examination.

Hypercoagulability risks in the patients with thromboembolic events were defined as elevated levels of fibrinogen; factors VIII, IX, and XI; decreased level of homocysteine (measured only in patients not receiving folic acid); proteins C and S; antithrombin-III and activated protein C (APC) resistance; factor II mutation; factor V-Leiden mutation; heterozygosity for 5 10-methylene tetrahydrofolate reductase (MTHFR) mutation; elevated levels of anti-phospholipids; including lupus anticoagulant (LAC), anticarboxypeptidase B (aCL), IgG, IgM, and IgA. Coagulation factors were measured at the time of diagnosis, and factors VIII, IX, and XI were measured again 3 to 6 months after diagnosis.

Fibrinogen and factors VIII, IX, and XI were determined using an agglutination pattern (ACL9000; International Laboratory Company; Lexington, MA). Homocysteine, protein C, antithrombin-III, and APC resistance were determined coagulometrically (ACL9000; International Laboratory Company). Free protein S antigen was determined by enzyme-linked immunosorbent assay (ELISA) [Diagnostic Reagents, Asnieres, France] and MTHFR mutation, factor II, and factor V-Leiden mutations were determined using the Pronto ThromboRisk primer-extension ELISA-based assay (Gamigadene; Rehovot, Israel). Antibodies against aCL-IgG and aCL-IgM were measured by ELISA kits (Pharmacia Diagnostics; Freiburg, Germany), as were antibodies against aCL-IgA (Reaads; Diapharma; West Chester, OH; BL-Diagnostica; Mainz, Germany). Anti-β2-glycoprotein I-IgG, IgM, and IgA were tested by three separate kits (Inova Diagnostics; San Diego, CA). LAC activity was determined by two different tests: dilute Russell viper venom time (LAC-RVVT; Gradipore; Frenchs Forest, Australia), and kaolin clotting time (LAC-KCT, Gradipore). Results for the LAC-RVVT test are recorded as negative, borderline, or positive. The positive value index for the LAC-KCT test is > 15%. Analysis includes screening and confirmation tests for both LAC assays.

Results

A total of 70 patients underwent lung transplantation during the study period. These included 49 male (70%) and 21 female patients aged 5 to 66 years. The primary disease for which the transplant was performed and the type of transplantation (one lung, double lung, heart-lung) are described in Table 1.

Thromboembolic complications developed in six patients (8.6%) after transplantation. Their characteristics are shown in Table 2. The thromboembolic event occurred 3 to 24 months after transplantation (mean time, 11 months) and consisted of DVT (two patients), PE (one patient), DVT and PE (one patient), and RVT (two patients). All six patients had been discharged from the hospital and were ambulatory at the time of the thromboembolic event, and they survived the complication. No patient had any sign of active infection by the time of diagnosis. All the patients presented with typical symptoms. Patients 1 and 2 presented with acutely reduced visual

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### Table 1—Primary Disease of Transplant Recipients (n = 70) by Type of Transplantation

<table>
<thead>
<tr>
<th>Primary Disease</th>
<th>Single Lung, No.</th>
<th>Bilateral Lung, No.</th>
<th>Heart-Lung, No.</th>
<th>Total, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD/emphysema</td>
<td>26</td>
<td></td>
<td></td>
<td>26 (37.2)</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>24</td>
<td>4</td>
<td>1</td>
<td>29 (41.4)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td></td>
<td></td>
<td>5</td>
<td>5 (7.1)</td>
</tr>
<tr>
<td>Bronchiectasis/cystic fibrosis</td>
<td>8</td>
<td>2</td>
<td></td>
<td>10 (14.3)</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>12</td>
<td>8</td>
<td>70 (100)</td>
</tr>
</tbody>
</table>

### Table 2—Characteristics of the Six Patients With Thromboembolic Complications Following Lung Transplantation

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Primary Disease</th>
<th>Transplantation</th>
<th>Age/Sex</th>
<th>Thrombotic Event</th>
<th>Time After Transplantation, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Emphysema</td>
<td>Right lung</td>
<td>62/male</td>
<td>RVT, left</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>Emphysema</td>
<td>Left lung</td>
<td>60/female</td>
<td>RVT, left</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>Fibrosis</td>
<td>Left lung</td>
<td>54/male</td>
<td>DVT, right</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Fibrosis</td>
<td>Left lung</td>
<td>55/male</td>
<td>PE</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Emphysema</td>
<td>Right lung</td>
<td>59/male</td>
<td>DVT, right</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>Emphysema</td>
<td>Left lung</td>
<td>62/female</td>
<td>DVT plus PE</td>
<td>9</td>
</tr>
</tbody>
</table>
acuity and blurred vision. Patients 3 and 5 complained about a swollen and painful right leg. Patient 4 came to the emergency department because of acute dyspnea, and patient 6 presented with pleuritic pain, dry cough, and dyspnea on effort. No other risk factors for thromboembolic disease (ie, prolonged trip, recent trauma or surgery, immobility) were present in any of our patients.

The results of the coagulation factor assays in the six patients are shown in Table 3, and the antiphospholipid measurements are shown in Table 4. The fibrinogen level was elevated in all six patients. Factors VIII, IX, and XI were elevated in five patients; all three factors were elevated in two patients. Two patients were heterozygous for the MTHFR mutation, and one patient each for factor II and factor V-Leiden mutation. Levels of protein C and protein S and APC resistance were within the normal range in all patients. Homocysteine was measured only in the three patients not receiving folic acid, and the levels were normal in all three patients. Four patients had mildly elevated levels of at least one antiphospholipid antibody. None had a positive LAC test result. Overall, all patients demonstrated abnormalities on hypercoagulability tests.

**Discussion**

The present study found that thromboembolic events occurred in 6 of 70 lung transplant recipi-
ents (8.6%) at 4 to 24 months after transplantation. A similar rate of posttransplantation PE (6 of 72 patients, 8.3%) was reported by Nathan et al in a single, tertiary-care, university-affiliated referral center. All PE events in that study occurred in the subgroup of patients with interstitial pulmonary fibrosis (n = 23). In our series, PE was diagnosed in only two patients, whereas the underlying disease was variable (Table 2). By contrast, the reported incidence of clinically significant PE in the general surgical population is as low as 1.6%. PE is probably also more frequent in transplant patients than in other specific surgical subgroups. Others reported even higher rates than those documented in the present series. Kroshus et al found an overall incidence of 12.1% for thromboembolic events in lung transplant recipients, and Burns and Iacono, in an autopsy study, noted a 27% rate in 126 lung and heart-lung transplant recipients.

Interestingly, in our study, all six affected patients had a hypercoagulable state, characterized by increased levels of coagulation factors (Table 3) or positive antiphospholipid antibodies (Table 4). Whether a hypercoagulable state is the main cause of the development of the thromboembolic complications and whether it is congenital or acquired remain unclear. We speculate that it may be acquired because none of the patients had a thromboembolic event prior to the transplantation, but no pretransplantation evaluation for hypercoagulability was done. As such, further studies are needed to determine if the hypercoagulability is related to the lung transplant itself, to the immunosuppressive treatment, to the underlying disease, or to another, unknown, cause. Elevated levels of factors VIII, IX, XI, and fibrinogen are known to be a risk factor for venous thrombosis. Factor VIII levels > 150 IU/dL are associated with a 4.8-fold higher risk of DVT than those with levels < 100 IU/dL, and fibrinogen levels above the 95th percentile of the distribution measured in control subjects have a 2.8-fold increased risk for a first DVT. But it is thought that elevated level of factor VIII and fibrinogen are in general not caused by acute-phase reactions. However, in a large scale study, the Longitudinal Investigation of Thromboembolism Etiology study, elevated fibrinogen levels did not predict an increased risk of venous thromboembolism. Furthermore, the presence of several hypercoagulability factors raises the risk of thrombosis, and all of our lung transplant patients in whom a thromboembolic event developed had at least two risk factors. Not only are DVT and PE known thromboembolic complications in patients with hypercoagulability, but also RVT. RVT, although less common, is also associated with hypercoagulable state, especially with hyperhomocysteinemia, protein S deficiency, and anticardiolipin antibodies.

Ducloux et al examined the prevalence and clinical significance of antiphospholipid antibodies in 178 renal transplant recipients with nonsystemic lupus erythematosus renal transplant cases. They found that 50 patients (28.1%) were positive for antiphospholipid antibodies, and they demonstrated more posttransplant venous and arterial thrombosis (18% vs 6.2%, p < 0.001%, and 8% vs 2.3%, p < 0.001, respectively). Indeed, hypercoagulability is now considered a grave risk factor for any potential solid-organ tissue transplant candidate. Studies of treatment with heparin, warfarin, and aspirin have yielded good results in the prevention of renal allograft thrombosis and graft loss.

Many issues still remain unanswered: should all lung transplant patients undergo investigations for thrombophilia before or after transplantation? Should prophylactic treatment be initiated in patients with hypercoagulability risk factors? How long should anticoagulation therapy be administered in patients after a thromboembolic event? Nevertheless, the results of the present study should prompt a higher index of suspicion in clinicians, which would lead to early diagnosis and successful treatment of these potentially fatal complications.

REFERENCES


