Lack of Left Ventricular Dysfunction Associated with Sustained Exposure to Hyperlipidemia Following Lung Transplantation*

Steven Kesten, MD, FCCP; Lisa Mayne, BSc; Mesina Scavuzzo, RN; and Janet Maurer, MD, FCCP

Objectives: Hyperlipidemia due to standard immunosuppressive agents occurs commonly following solid organ transplantation. A decision to treat hyperlipidemias would be based on the assumption that such disorders lead to accelerated atherogenesis and ultimately to cardiac dysfunction. We therefore sought to examine whether hyperlipidemias following lung transplantation were associated with a decline in left ventricular (LV) function.

Study design: We retrospectively reviewed serial echocardiograms, radionucleotide angiograms (RNAs), and serum lipid levels following lung transplantation. Results of cardiac studies were defined as abnormal if a decline in LV grade occurred from the best result at any time postoperatively to the most recent study.

Patients: A total of 184 patients with transplants between November 1983 and June 1995 were reviewed. Eighty patients were excluded owing to incomplete data. One patient was excluded because of severe perioperative myocardial dysfunction.

Results: Approximately 80% of patients had elevated cholesterol levels and 60% had elevated low-density lipoprotein levels. Triglyceride levels were raised in 34% of patients while only 4% had an abnormal serum high-density lipoprotein level. More than 80% of patients had no evidence of LV abnormalities in either RNA or echocardiographic studies (group 1). One patient had a change in echocardiographic LV function but no change in grade of RNA (group 2). Twenty patients had a decline in grade based on RNA but no change in the echocardiogram (group 3). There were no patients with changes in both RNA and echocardiogram (group 4). All changes in LV function were from grade I to II. The mean period of follow-up exceeded 30 months for patients in groups 1 to 3. Follow-up data at 3, 4, and 5 years were available on 47, 23, and 12 patients, respectively. There were no differences between the proportions of subjects with normal and abnormal serum lipid levels in each group.

Conclusions: In the initial 5 years after lung transplantation, dyslipidemias affect the majority of patients but are not associated with evidence of deteriorating LV function.

(CHEST 1997; 112:931-36)

Key words: atherosclerosis; cyclosporine; hyperlipidemia; lung transplantation

Abbreviations: HDL=high-density lipoprotein; LDL=low-density lipoprotein; LV=left ventricular; RNA=radionucleotide angiogram

Hyperlipidemias have been identified as risk factors for ischemic heart disease through accelerated atherosclerosis.1 Extended efforts have therefore been directed toward identifying populations at risk in order to initiate management strategies that vary from dietary modifications alone to the regular administration of lipid-lowering agents. Altering serum lipids toward normal levels through medication has been demonstrated to reduce atherosclerotic lesions in patients who have not received transplanted organs.2,3 These agents have also been demonstrated to reduce the incidence of cardiovascular events.4 While genetic background and diet influence serum lipid levels, attention has also focused on medications that have the potential for altering lipids in an adverse manner.5,6 Such medications include

*From Rush-Presbyterian-St. Luke’s Medical Center, Chicago and The Toronto Hospital, Toronto, Ontario, Canada.

Manuscript received October 23, 1996; revision accepted May 22, 1997.

Reprint requests: Steven Kesten, MD, FCCP, Rush-Presbyterian-St. Luke’s Medical Center, 1725 W Harrison St, Suite 836, Chicago, IL 60612; email: skesten@rush.edu
β-blockers and diuretics. Advertisements for these medications occasionally emphasize their lack of lipid-altering effects, suggesting that doing so is clinically meaningful.

Cyclosporine is the single most important immunosuppressive development in the field of solid organ transplantation. It is associated with improvements in graft viability in many organ systems but has multiple adverse effects. One common effect is to alter serum lipids, including raising serum cholesterol levels. Transplant recipients often receive systemic steroids in addition to cyclosporine, which may also influence serum lipids. However, Stillner et al noted a rise in serum triglyceride and cholesterol levels shortly after treatment with cyclosporine alone was started for the treatment of severe psoriasis.

It remains speculative whether dyslipidemias secondary to medications such as cyclosporine are clinically relevant for the noncardiac transplant patient without a history of atherosclerosis. If specific interventions are recommended for lowering cyclosporine-associated abnormal serum lipid levels, it would be on the assumption that sustained exposure to the dyslipidemia results in clinical manifestations that would lead to increased morbidity and mortality in the transplant recipient. Perhaps the most common adverse manifestation of dyslipidemia is ischemic heart disease. We therefore sought to evaluate whether any measurable changes in left ventricular (LV) function have occurred over time in our lung transplant recipients that could be associated with a sustained disorder of serum lipids.

**Materials and Methods**

**Study Population**

All patients who received lung allografts between November 1983 and June 1995 were included in the study. Patients were excluded due to incomplete laboratory data. Patients selected for lung transplantation were vigorously screened for evidence of disease in other solid organs. The routine transplant assessment included serum liver enzymes, urea, creatinine, 24-h urine for creatinine clearance, ECG, echocardiogram, and a radionucleotide angiogram (RNA). Abnormal liver or renal function was considered exclusionary. Suspicion of ischemic heart disease from history or routine cardiac imaging led to further investigations, including the liberal use of cardiac catheterization when necessary. Patients were not accepted for transplantation if they had documented ischemic heart disease. Serum triglyceride, cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels were measured preoperatively, but abnormalities in lipid profile did not in themselves constitute an exclusionary criteria.

**Posttransplant Assessments**

In addition to minor assessments (ie, clinic visit, biochemistry, cyclosporine levels), full assessments are scheduled for each transplant recipient at 3, 6, 9, 12, 18, and 24 months and yearly thereafter. During the full assessments, patients have blood work, including triglyceride, cholesterol, LDL, and HDL as well as fiberoptic bronchoscopy with transbronchial biopsies, chest radiograph, CT thorax, pulmonary function tests, ECG, echocardiogram, and an RNA.

**Immunosuppression Regimen Posttransplant**

Patients were maintained on a regimen of cyclosporine, azathioprine, and prednisone. Whole blood trough levels were maintained between 250 and 350 ng/mL over the initial 3 months and gradually reduced to between 150 and 250 ng/mL after approximately 1 year. Azathioprine was prescribed at approximately 1 mg/kg/d but dosage was reduced if liver enzyme abnormalities or leukopenia occurred. Prednisone was initially given at approximately 0.5 mg/kg/d and reduced gradually until 1 year when the dose was 15 mg every other day indefinitely. Episodes of acute rejection were treated with methylprednisolone, 1 g IV daily for 3 days followed by prednisone, 40 mg daily. The augmented prednisone dose was reduced to baseline over 3 to 4 weeks.

**Data Collection**

Medical records of all patients who had undergone transplantation were reviewed. Demographics of the patient, serum levels of triglyceride, cholesterol, LDL, and HDL, as well as echocardiogram results and rejection fractions from RNA were recorded. The means of all posttransplant lipid values were calculated for each patient. The lipid concentration was scored as normal or abnormal based on the mean posttransplant values. Patient records were searched for documentation of ischemic heart disease and cardiovascular procedures for ischemic heart disease. The following definitions were used for classification of results: normal echocardiogram—no change in LV grade from the known best posttransplant to the last available result; normal RNA—no change in RNA LV grade from the known best posttransplant to the last available result. Tables 1 and 2 show values for normal serum lipid levels and LV ejection fraction, respectively.

**Categorization of Tests of LV Function**

As we relied on two noninvasive tests of LV function as surrogate markers of ischemic events, a liberal system was

<table>
<thead>
<tr>
<th>Table 1—Normal Serum Lipid Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2—LV Ejection Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>
developed to increase the sensitivity of finding a potential change in LV function. Results of cardiac studies were defined as abnormal if a decline in LV grade occurred from the best result at any time postoperatively to the most recent study at the time of data collection. The patients were divided into the groups as shown in Table 3.

Data Analysis

Data are expressed as absolute numbers or proportions in each of the categories listed. Values for lipids are expressed as mean±SD. The differences in proportion of subjects in the aforementioned groupings of cardiac tests were compared through χ² analysis. Statistical significance was set at p<0.05.

RESULTS

Study Population

A total of 184 patients were identified. Follow-up data were insufficient in 39 patients. RNA or echocardiographic data were incomplete in 30 patients. Serum lipid data were incomplete in 11 patients. One patient had severe LV damage during surgery and was excluded. Hence a total of 103 patients were included in the analysis. There were 48 women and 55 men with a mean age of 45.9±12.4 years.

Lipid Abnormalities

Approximately 80% of patients had elevated cholesterol levels and 60% had elevated LDL levels. Triglyceride levels were raised in 34% of patients while only 4% had an abnormal serum HDL level. When present, abnormalities in serum lipid levels were virtually always present at the initial posttransplant evaluation (ie, 3 months). The mean values for serum lipids were as follows: (1) cholesterol, 6.12±1.14 mmol/L; (2) triglycerides, 2.08±0.74 mmol/L; (3) LDL, 3.58±1.04 mmol/L; and (4) HDL, 1.56±0.42 mmol/L.

Lipid-Lowering Medication Interventions

During the period of study, 13 of the 103 patients received trials of lipid-lowering agents. The agents used included cholestyramine, lovastatin, probucol, and gemfibrozil. Ten patients received therapy for <1 year; seven were treated for no more than 6 months. Of those treated for >1 year, one was treated with cholestyramine for 43 months, one with gemfibrozil for 14 months, and the third with gemfibrozil and then probucol for a total of 17 months. The majority of the group had treatment discontinued due to lack of efficacy or adverse effects.

Categorization of LV Function

The mean period of follow-up exceeded 30 months for patients in groups 1 to 3 (Table 4). Follow-up data at 3, 4, and 5 years were available on 47, 23, and 12 patients, respectively. Over 80% of patients had no evidence of LV abnormalities in either RNA or echocardiographic studies (group 1). One patient had a change in echocardiographic LV function but no change in grade of RNA (group 2). Twenty patients had a decline in grade based on RNA but no change in the echocardiogram (group 3). There were no patients with changes in both RNA and echocardiogram (group 4). All changes in LV function were from grade I to II. The mean follow-up in the groups in which functional changes possibly occurred were 48 months in group 2 and 29 months in group 3. The number of subjects with abnormal serum lipid levels according to LV imaging studies (ie, group) is listed in Table 5.

There were no differences between the proportions of subjects with normal and abnormal serum lipid levels in each group (Figs 1-4).

Clinical Evidence of Ischemic Heart Disease

Two men, one with a strong family history, developed coronary artery disease. No deaths have occurred due to ischemic heart disease.

Table 3—Groups of Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Echo</th>
<th>RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>4</td>
<td>Abnormal</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>

Table 4—Length of Follow-up of 103 Lung Transplant Recipients

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Months Posttransplant</th>
<th>No. of Subjects According to Years Posttransplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n=82)</td>
<td>32.91</td>
<td>1</td>
</tr>
<tr>
<td>2 (n=1)</td>
<td>48</td>
<td>1</td>
</tr>
<tr>
<td>3 (n=20)</td>
<td>34.95</td>
<td>17</td>
</tr>
<tr>
<td>4 (n=0)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Dyslipidemias following solid organ transplantation are a common and well-described phenomenon. The use of immunosuppressive medications has been associated with such changes. Approximately 60 to 80% of cardiac transplant recipients are noted to have hypercholesterolemia. In cardiac transplantation, dyslipidemias appear to be associated with accelerated graft atherosclerosis, although accelerated atherosclerosis is also a manifestation of chronic allograft rejection. It therefore seems reasonable to treat dyslipidemias aggressively in cardiac transplant recipients. However, the correct strategy toward treatment of lipid abnormalities in other organs is unclear. In our center, a high proportion of lung allograft recipients have elevations in serum cholesterol and LDL levels while approximately one third have raised serum triglyceride levels. Nevertheless, relatively few patients have deteriorations in LV function posttransplant by either echocardiogram or RNA and none have evidence of a deterioration in both studies. Only two people (<2%) had clinical evidence of coronary artery disease.

In renal allograft recipients, Kuster et al noted that cyclosporine blood levels were correlated to total plasma cholesterol and the cholesterol/HDL cholesterol ratio although not to plasma triglycerides. Inverse correlations were seen with HDL cholesterol, LDL 3 cholesterol, and apolipoprotein A-1. These findings are consistent with a pattern of lipid disorders associated with atherosclerosis. Furthermore, the abnormalities in lipid levels appear sustained. Sharma et al found hypercholesterolemia in 17 of 33 adolescent and adult renal transplant patients who had received their transplant an average of 6.4 years earlier. Of note, no difference was seen in lipid profiles in the patients receiving prednisone-azathioprine vs prednisone-azathioprine-cyclosporine, although this may have simply reflected their sample size. Yet in a study of the use of cyclosporine in 22 patients with psoriasis in which no prednisone or azathioprine was administered, serum triglyceride level rose from 118 to 184 mg/dL and cholesterol

Table 5—Frequency of Lipid Abnormalities in 103 Lung Transplant Recipients

<table>
<thead>
<tr>
<th>Group</th>
<th>Cholesterol</th>
<th>Triglycerides</th>
<th>LDL</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Norm*</td>
<td>Abn*</td>
<td>Norm</td>
<td>Abn</td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>66</td>
<td>54</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>16</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Norm=normal; Abn=abnormal.

FIGURE 1. Proportion of lung transplant recipients with normal and proportion with abnormal serum cholesterol levels according to group.

FIGURE 2. Proportion of lung transplant recipients with normal and proportion with abnormal serum triglyceride levels according to group.
level rose from 207 to 247 mg/dL after 2 weeks of treatment and remained elevated for the 12 to 16 weeks of treatment.8

The issue of adverse clinical outcomes associated with hyperlipidemia following solid organ transplantation is far from straightforward. Several other factors must be considered. Hypertension, which is a risk factor for coronary artery disease, is another adverse effect associated with cyclosporine. The interplay of hypertension and drug-induced lipid abnormalities on atherosclerosis is unclear. Systemic steroids also adversely influence serum lipid profiles. In a study of 25 renal transplant recipients treated with steroids and azathioprine (not cyclosporine), 44% had increased serum triglyceride levels between 1.5 and 3 years posttransplant.16 Animal studies may aid in dissecting out confounding variables. Experiments in mice suggest that under the right circumstances, cyclosporine may promote atherogenesis. Mice fed an atherogenic diet plus cyclosporine developed larger atherosclerotic lesions than mice given the same diet without cyclosporine.17 Nevertheless, the effects of hyperlipidemia on long-term clinical outcome (which in transplantation is measured in years rather than decades) must ultimately be addressed. A recent review of hyperlipidemia postrenal transplant suggested that hyperlipidemia is an important metabolic consequence that affects "long-term patient survival unless recognized and treated."18 However, the same author documented no cardiovascular deaths and no excess in graft loss in a 4-year follow-up of renal transplant patients with early hyperlipidemia.19

Hyperlipidemia posttransplant can successfully be treated with lipid-lowering agents. Simvastatin at 10 mg/day was associated with a 12.5% decrease in cholesterol level and a 21.3% decrease in LDL level after 4 months of treatment in 20 hypercholesterolemic heart transplant patients.20 Simvastatin was also associated with a 28.7% increase in alanine aminotransferase concentrations. If hyperlipidemia requires treatment, one approach might be to convert to an alternate immunosuppressive agent without the same dyslipidemic effects, thereby avoiding potential adverse effects from lipid-lowering agents. In a report of seven subjects, conversion from cyclosporine to tacrolimus (FK 506) was associated with reduced plasma cholesterol, LDL, and triglyceride levels.21 Lower mean cholesterol levels with pravastatin were noted in a study of 97 cardiac allograft recipients randomized to pravastatin or no pravastatin.22 Perhaps the most provocative findings in the pravastatin study were the association of reduced coronary vasculopathy and rejection causing hemodynamic compromise in the pravastatin-treated group, suggesting the possibility of useful immunosuppressant properties of β-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.22 Further studies involving patients receiving noncardiac allografts need to be considered.

We recognize that our study has several limitations. We did not directly examine for coronary artery disease. The most definitive test would be to perform coronary angiography. As well, we did not test for the presence or absence of reversible ischemic areas as assessed by dipyridamole (Persantine) or exercise thallium studies. However, we attempted to bias the study in favor of showing an association of hyperlipidemia with impaired LV function by assessing two separate imaging methods. As well, we used the best rather than the average result of previous tests as the study to compare to the most recent

Figure 3. Proportion of lung transplant recipients with normal and proportion with abnormal serum LDL levels according to group.

Figure 4. Proportion of lung transplant recipients with normal and proportion with abnormal serum HDL levels according to group.

Downloaded From: http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21752/ on 06/26/2017
evaluation. It is also possible that our duration of follow-up is insufficient. Lesions in noncardiac transplant recipients might require decades to develop. Nevertheless, given that 5-year survival following lung transplant is no better than 50% and given the potential adverse systemic effects, added problems to compliance, and additional costs of lipid-lowering agents, our information may open the debate about the necessity of intervening with drugs or difficult-to-follow dietary restrictions.

It should be noted that the mean increases in cholesterol and LDL levels after transplantation are modest and it is therefore not surprising that they do not appear to be associated with cardiac dysfunction. Again, this observation emphasizes the need to exercise caution in overzealous lipid-lowering medication prescriptions.

There are no clinical studies in human subjects to date (and to our knowledge) that suggest drug-induced dyslipidemias lead to accelerated coronary artery disease in noncardiac transplant recipients. Furthermore, many centers deny the opportunity of lung transplantation to individuals with documented heart disease. The possibility of existing ischemic heart disease is virtually eliminated in candidates through aggressive imaging techniques that may include coronary angiography (i.e., in older subjects with an extensive smoking history). By such screening, lung transplant programs generally eliminate individuals who are genetically predisposed to coronary artery disease. It is likely that hyperlipidemia in such individuals, particularly if drug induced, has a different implication than in those who may be genetically predisposed to atherosclerosis. The present study suggests that while hyperlipidemias are extremely common and sustained in lung transplant recipients, they are not associated with adverse changes in LV function in the first 5 years post transplant. As physicians, we try to maintain the stand of *primum non nocere* and until we know otherwise, perhaps we should not be overly aggressive in the treatment of dyslipidemias in patients who receive lung allografts.

**References**

4. The Pravastatin Multinational Study Group for Cardiac Risk Patients. Effects of pravastatin inpatients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. Am J Cardiol 1993; 72:1031-37
17. Emison EE, Shen ML. Accelerated atherosclerosis in hyperlipidemic C57BL/6 mice treated with cyclosporin A. Am J Pathol 1993; 142:1906-15