Is Routine Coronary Angiography and Revascularization Indicated Among Patients Undergoing Evaluation for Lung Transplantation?*

Itsik Ben-Dor, MD; David Shitrit, MD; Mordechai R. Kramer, MD, FCCP; Zaza Iakobishvili, MD, PhD; Gideon Sahar, MD; and David Hasdai, MD

**Objectives:** To review coronary artery disease (CAD) prevalence among lung transplantation (LTx) candidates, the time interval from coronary angiography (CA) to LTx/death, and postrevascularization outcomes.

**Background:** CA is advised for LTx candidates because significant CAD is a contraindication for LTx.

**Methods:** We monitored all LTx candidates from 1997 who underwent CA. Significant CAD was defined as stenosis ≥ 70% in diameter.

**Results:** Of 118 candidates >40 years old (68.3% men; median age, 58 years; 25 to 75th interquartiles, 53 to 61 years), 59 patients underwent LTx, 56 patients were eligible for LTx, and 3 patients were excluded due to CAD. Significant CAD was detected in 21 patients (17.8%), nonsignificant CAD was found in 21 patients (17.8%), and no CAD was found in 76 patients (64.4%), without significant differences in the demographic/clinical profile among patients with or without significant CAD. Among 21 patients with significant CAD, 12 patients (57.1%) underwent successful percutaneous coronary intervention (PCI), 1 patient had failed to respond to PCI, and 8 patients (38.1%) had no intervention. After PCI, one patient had periprocedural infarction, one patient had stent thrombosis, and one patient had symptomatic restenosis. The median time interval CA to LTx/death/last visit among the 115 candidates was 166 days (interquartiles, 48 to 410 days). Death occurred before LTx in 30 patients (53.5%) during a follow-up of 312 days (interquartiles, 46 to 664 days) and after LTx in 14 patients (23.7%) during a follow-up of 142 days (interquartiles, 73 to 304 days), without any difference in outcome based on severity of CAD in the two groups (p = 0.7 and p = 0.6, respectively).

**Conclusions:** CAD prevalence among LTx candidates is low and cannot be accurately predicted by risk factors. Revascularization may be associated with complications, and the time interval between revascularization and LTx may be long. Conversely, certain patients with significant CAD underwent LTx without complications. The practice of routine CA and revascularization prior to LTx should be reconsidered, and perhaps reserved for selected patients with high-risk features.

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**Key words:** coronary angiography; coronary artery disease; lung; transplantation; revascularization

**Abbreviations:** CA = coronary angiography; CAD = coronary artery disease; LTx = lung transplantation; LV = left ventricular; PCI = percutaneous coronary intervention

Lung transplantation (LTx) has emerged as a successful therapeutic modality for end-stage pulmonary disease in recent years. Because of the scarcity of donor lungs, patients referred for LTx are carefully screened for concomitant medical problems that might compromise their success of the transplant surgery or limit their survival after surgery. Selection criteria for placement on the active waiting list for LTx vary between centers, but the presence of significant coronary artery disease (CAD) or left ventricular (LV) dysfunction has traditionally been considered a contraindication to

*From the Departments of Cardiology (Drs. Ben-Dor, Iakobishvili, and Hasdai), Pulmonology (Drs. Shitrit and Kramer), and Cardiothoracic Surgery (Dr. Sahar), Rabin Medical Center, Petah Tikva, and Tel Aviv University, Tel Aviv, Israel. Manuscript received January 18, 2005; revision accepted April 7, 2005.*

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Correspondence to: David Hasdai, MD, Department of Cardiology, Rabin Medical Center, 39 Jabotinsky St, Petah Tikva, Israel 49100; e-mail: dhasdai@post.tau.ac.il.
LTx. The current guidelines for the evaluation of LTx candidates recommend stress echocardiography and/or coronary angiography (CA) in patients at high risk for CAD, but the widespread practice in most LTx centers is the referral for routine CA of all patients > 40 to 45 years age or with coronary risk factors. CA is an invasive procedure that portends certain rare, yet significant, risks, and its yield in this patient population is uncertain. The routine use of CA as a screening tool in the pre-LTx setting has been challenged by four small, prior studies because the incidence of significant CAD in these studies was only 4 to 16%. Furthermore, there are limited data regarding the time interval between CA with or without revascularization and the performance of LTx. If this time interval is relatively long, the pertinence of CA or revascularization may be dubious, given the natural progression of CAD and the possibility for restenosis. The aim of our study was to review CAD prevalence among LTx candidates, the time interval from CA to LTx or death, and postrevascularization outcomes.

**Materials and Methods**

We performed a thorough retrospective review of the medical records of all LTx candidates at Rabin Medical Center during the years 1997 through 2004 who underwent CA during their pre-LTx evaluation. At our center, the criteria for referral for CA include age > 50 years, cardiac symptoms, or significant risk factors for CAD. Candidates with CAD who the attending physician considered to have high-risk features and who did not undergo revascularization or were not planned for revascularization during LTx were excluded from the LTx list.

The data analyzed included demographic, clinical, echocardiographic LV function, right-heart catheterization, and coronary artery variables. Revascularization procedures and complications were reviewed. Significant CAD was defined as a diameter stenosis ≥ 70% in a major epicardial coronary artery.

**Statistical Analysis**

Statistical analysis was done using statistical software (SPSS version 11; SPSS; Chicago, IL). Continuous variables are expressed as median (25 to 75th interquartiles). Differences between continuous variables were assessed by using Student t test or analysis of variance. Categorical variables were compared using the χ² test. Significance was set at p < 0.05. Bivariate correlations were assessed using the bivariate correlation test. Long-term survival was assessed using the log-rank statistic.

**Results**

Our cohort included 118 LTx candidates > 40 years old, 68.3% of whom were men (Table 1). Median age was 58 years (range, 53 to 61 years). Of the 118 patients, 39 subsequently underwent LTx (50.0%), 56 remained LTx candidates (47.4%), and 3 were excluded due to CAD (2.6%) [Fig 1]. Of the three patients who were excluded, two had three-vessel CAD, and one had two-vessel CAD. Significant CAD was detected in 21 candidates (17.8%), nonsignificant CAD was found in 21 patients (17.8%), and anatomically normal coronary arteries were found in 76 patients (64.4%).

There were no significant differences in the demographic or clinical profile among patients with or without CAD, except for fewer men in the normal coronary artery group (p = 0.03) and more diabetes mellitus among patients with significant CAD (p = 0.04) [Table 1]. However, > 50% of the patients in the normal coronary artery group were men, and approximately one fourth had diabetes mellitus.

Maximal oxygen consumption was severely reduced in our cohort (Table 2). Pulmonary hypertension was not significantly high in the majority of patients. The LV function of patients with significant CAD was significantly lower compared to others (p < 0.001), yet two thirds of the patients with significant CAD had good LV function.

The causes of end-stage lung disease were COPD in 52 patients (44.1%), idiopathic pulmonary fibrosis in 59 patients (50.0%), and other causes in 7 patients (5.9%) [pulmonary hypertension, n = 3; bronchiectasis, n = 3; and histiocytosis, n = 1]. There was no difference in CAD prevalence among the various etiologies of lung disease.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No CAD</th>
<th>Nonsignificant CAD</th>
<th>Significant CAD</th>
<th>All Patients</th>
<th>p Value</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>76 (64.1)</td>
<td>21 (17.8)</td>
<td>21 (17.8)</td>
<td>118 (100)</td>
<td>0.18</td>
<td>0.37</td>
</tr>
<tr>
<td>Age, yr</td>
<td>56 (53.0–59.0)</td>
<td>60 (57.0–62.0)</td>
<td>60 (55.0–64.5)</td>
<td>58 (53–61)</td>
<td>0.18</td>
<td>0.37</td>
</tr>
<tr>
<td>Male gender</td>
<td>43 (56.5)</td>
<td>18 (85.7)</td>
<td>19 (90.4)</td>
<td>80 (68.3)</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18 (23.6)</td>
<td>3 (14.2)</td>
<td>8 (38.0)</td>
<td>29 (24.7)</td>
<td>0.09</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (28.9)</td>
<td>7 (33.3)</td>
<td>9 (9.4)</td>
<td>38 (32.4)</td>
<td>0.50</td>
<td>0.26</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>14 (18.4)</td>
<td>4 (19.0)</td>
<td>7 (33.3)</td>
<td>25 (21.3)</td>
<td>0.33</td>
<td>0.14</td>
</tr>
<tr>
<td>Smoking</td>
<td>52 (68.4)</td>
<td>15 (71.4)</td>
<td>18 (85.7)</td>
<td>85 (72.6)</td>
<td>0.30</td>
<td>0.14</td>
</tr>
<tr>
<td>Prior CAD</td>
<td>0</td>
<td>3 (14.2)</td>
<td>4 (19.0)</td>
<td>7 (5.0)</td>
<td>0.001</td>
<td>0.006</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.1 (23.4–30.8)</td>
<td>25.9 (24.5–29.2)</td>
<td>26.0 (22.4–30.8)</td>
<td>26.1 (23.5–30.8)</td>
<td>0.61</td>
<td>0.54</td>
</tr>
</tbody>
</table>

*Data are presented as mean (25 to 75th interquartiles) or No. (%).
†No CAD and nonsignificant CAD vs significant CAD.
Among the 21 patients with significant CAD, 12 patients (57.1%) underwent successful percutaneous coronary intervention (PCI), 1 patient had failed to respond to PCI, and 8 patients (38.1%) had no intervention (total occlusion, n = 3; distal disease, n = 3; collateral circulation, n = 1; planned coronary artery bypass grafting surgery combined with LTx, n = 1). Of the 12 PCI patients, 5 subsequently underwent LTx. Of the eight conservatively treated patients, three subsequently underwent LTx. Of the post-PCI patients, one had a periprocedural myocardial infarction, one had a subacute stent thrombosis 1 month after intervention before LTx, and one had symptomatic in-stent restenosis 7 months after PCI and 3 months after LTx.

The median time intervals from CA to LTx/death/last visit among the 115 eligible candidates was 166 days (interquartiles, 48 to 410 days); 174 days (interquartiles, 124 to 369 days) among patients with significant CAD, and 124 days (interquartiles, 100 to 173 days) among patients after successful PCI.

Death occurred while on the waiting list after CA in 30 patients (53.5%) during a median follow-up of 312 days (interquartiles, 46 to 664 days) and after LTx in 14 patients (23.7%) during a median follow-up of 142 days (interquartiles, 73 to 304 days), without any difference in outcome based on severity of CAD in the two groups (Fig 2).

**DISCUSSION**

**Yield of Routine CA**

Our study of 118 patients with end-stage lung disease being considered for LTx demonstrates a prevalence of significant CAD of only 17.8% among candidates who underwent CA. This low prevalence is in accordance with previous, smaller trials that reported a prevalence of 4 to 16%. Thus, the yield of routine CA among LTx candidates is questionable.

**Current Practice and Guidelines**

The current guidelines for the evaluation of LTx candidates recommend stress echocardiography and/or CA for candidates at high risk for CAD, but the current practice of many LTx centers is routine CA. Several programs perform CA in all patients >40 to 50 years of age regardless of the coronary risk factor profile. Other programs reserve CA for patients believed to be at high risk for CAD on the basis of their risk factor profile. Others include the results of transthoracic echocardiography in their decision algorithm; the decision to perform CA is based on the echocardiographic findings and risk factor profile. In our center, the decision to perform CA is based on age, symptoms, or risk factor profile.

**Noninvasive Tests for Ischemia**

The current cardiology guidelines for perioperative cardiovascular evaluation for noncardiac surgery consider CA as a class III indication for LTx.

**Table 2—Hemodynamic Parameters**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No CAD</th>
<th>Nonsignificant CAD</th>
<th>Significant CAD</th>
<th>All</th>
<th>p Value</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No. (%)</td>
<td>76 (64.1)</td>
<td>21 (17.8)</td>
<td>21 (17.8)</td>
<td>118 (100)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Good LV function, No. (%)</td>
<td>73 (96.0)</td>
<td>19 (90.4)</td>
<td>14 (66.6)</td>
<td>105 (89.7)</td>
<td>0.81</td>
<td>0.87</td>
</tr>
<tr>
<td>Oxygen consumption, mL/kg/min</td>
<td>9.8 (2.7)</td>
<td>10 (4.9)</td>
<td>10 (2.4)</td>
<td>9.9 (3.3)</td>
<td>0.66</td>
<td>0.66</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>5.2 (1.7)</td>
<td>5.2 (1.8)</td>
<td>4.9 (1.7)</td>
<td>4.8 (1.6)</td>
<td>0.66</td>
<td>0.66</td>
</tr>
<tr>
<td>Cardiac index, L/min/body surface area</td>
<td>2.9 (0.9)</td>
<td>2.5 (0.8)</td>
<td>2.5 (0.4)</td>
<td>2.7 (0.8)</td>
<td>0.68</td>
<td>0.68</td>
</tr>
<tr>
<td>Mean pulmonary pressure, mm Hg</td>
<td>29.1 (9.8)</td>
<td>26.3 (7.0)</td>
<td>26.1 (8.5)</td>
<td>28 (9.1)</td>
<td>0.22</td>
<td>0.31</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mm Hg</td>
<td>14.5 (6.3)</td>
<td>12.7 (4.6)</td>
<td>11.7 (5)</td>
<td>13.7 (5.8)</td>
<td>0.07</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD) unless otherwise indicated.
†No CAD and nonsignificant CAD vs significant CAD.
candidates > 40 years old unless noninvasive testing for cardiac ischemia is highly positive. However, noninvasive testing may be inadequate to exclude significant CAD in this population. Exercise testing is of little value because exertion tolerance is limited by pulmonary disease, dipyridamole scanning cannot be used in the presence of theophylline therapy and is contraindicated in severe obstructive lung disease, and dobutamine thallium scanning has limited specificity and unknown sensitivity in this patient population. Thus, noninvasive tests for ischemia may be of limited benefit in this patient population.

It is worth mentioning that noninvasive imaging techniques to image the coronary arteries, such as multislice coronary CT or MRI are currently being introduced into clinical practice. Although these techniques may also portend certain risks, such as contrast-induced renal failure using CT, they spare the risks associated with an invasive technique. Thus, using these noninvasive techniques, the yield of detecting significant CAD in only 17.8% of the LTx candidates may be more justifiable.

**Other Predictors of CAD**

Although studies have reported coronary risk factors to have clinically useful predictive power to indicate which patients should undergo CA, in our cohort we found only male gender and diabetes mellitus more frequent among patients with significant CAD. However, it is notable that half the patients with normal coronary arteries were men and one fourth had diabetes mellitus. Thus, the discriminatory value of these two parameters is limited. Possibly with a larger sample size we would be able to detect statistically significant differences in the prevalence of certain risk factors between patients with and without significant CAD, but still a substantial proportion of patients with these risk factors would not be expected to have significant CAD. Similarly, although echocardiographic studies of LV size and function were more commonly abnormal among patients with significant CAD, 66.6% of patients with significant CAD had normal LV function.

**The Dilemma of Revascularization**

The dilemma of whether to perform CA extends to the dilemma of whether revascularization should be performed in asymptomatic, high-risk patients. The presence of CAD in patients undergoing noncardiac surgery places them at risk for perioperative or postoperative ischemic heart events. The role of prophylactic preoperative coronary intervention in reducing perioperative cardiac complications remains unclear. No randomized clinical trial (to our knowledge) has demonstrated a benefit offered by prophylactic PCI with balloon angioplasty, stents, or other devices before noncardiac surgery in reducing perioperative ischemia or myocardial infarction. Moreover, the complication rate of revascularization may be higher than expected in high-risk popula-
tions. Indeed, in our cohort, 3 of the 13 patients (23.0%) who underwent revascularization had complications (periprocedural myocardial infarction, stent thrombosis, and in-stent restenosis).

In the era of increased use of drug-eluting stents during PCIs, the dilemma of revascularization may be further sharpened. The use of drug-eluting stents may significantly reduce the restenosis rate, thus increasing the chance that the treated artery will remain patent until LTx is performed. However, because intense and prolonged antithrombotic treatment is recommended after the implantation of drug-eluting stents, often precluding the performance of surgical procedures, including transplantations, the LTx procedure may also be delayed for 3 to 6 months. A candidate may therefore potentially have to forego a LTx because of a recent PCI.

Time Interval

The time interval was long between revascularization and LTx (124 days; interquartiles, 100 to 173 days), enough for restenosis to occur or for CAD to progress. Moreover, after CA, the median time interval to LTx/death/last visit was 166 days, and elsewhere the waiting period may approach 2 years.2 Thus, the results of the index CA may be irrelevant at the time of LTx, given the significant time interval.

Is CAD a Contraindication for LTx?

The presence of significant CAD or LV dysfunction has traditionally been considered a contraindication to LTx.1,2,17,18 The International Lung Transplant Registry describes an approximate 11% mortality perioperative and an approximate 5% mortality at 1 year in LTx recipients due to CAD.19 Cardiovascular comorbidities were the most frequent reason for rejecting patients from the candidate list.20 In our study, of the 21 patients with significant CAD, 8 patients underwent LTx. Coronary revascularization was performed in five patients prior to LTx, and three patients with significant CAD underwent LTx without revascularization, of whom one patient died 1 month after LTx, not due cardiac cause. Other studies21,22 reported that coronary revascularization allows patients to undergo LTx with an acceptable outcome.

Death occurred while on the waiting list after CA in 30 patients (53.3%) during a median follow-up of 312 days, and after LTx in 14 patients (23.7%) during a median follow-up of 142 days, without any difference in outcome based on severity of CAD in the two groups. These rates are in accordance with the rates reported by others.19,20 However, it is important to stress that given the small number of LTx patients with significant CAD who did or did not undergo revascularization, our results should be interpreted with caution.

These results also indicate that a substantial proportion of patients who undergo pre-LTx CA do not survive > 1 year after the CA, highlighting the high-risk profile of this patient population. Moreover, these findings, demonstrating that the outcomes before and after LTx are not influenced by the presence of CAD, cast a serious doubt regarding the need to revascularize these patients prophylactically, especially given their high-risk profile.

An alternative approach is to revascularize the patient during LTx. In our institution, no patient had LTx combined with coronary artery bypass grafting, and one candidate planned for this approach died while on the waiting list. There are two reports21,23 of several patients who underwent successful LTx concomitant with bypass surgery. Coronary grafting at the time of LTx may prolong the procedure due to institution of cardiopulmonary bypass, possibly causing early graft dysfunction,24 although this concern has been refuted by others.25 If an approach of revascularization performed concomitantly with LTx is pursued, it is important that the time interval from CA to LTx be relatively short (up to 1 year), so that the results of the CA will remain relevant for guiding revascularization.

Thus, our study does not resolve the question of who should undergo revascularization or when or, conversely who should be excluded from the LTx list due to CAD. However, our findings do challenge the current practice of routine revascularization of LTx candidates with CAD as a prerequisite for their inclusion on the LTx list. Further studies are needed to determine the optimal mode of revascularization and its timing in this patient population.

Conclusion

The prevalence of significant CAD among LTx candidates is low and cannot be accurately predicted by risk factors. Revascularization may be associated with complications, and the time interval from revascularization to LTx may be long. Conversely, certain patients with significant CAD underwent LTx without complications. We suggest that the practice of routine CA and revascularization prior to LTx should be reserved for patients with selected high-risk features, such as patients with significant LV dysfunction or objective evidence of ischemia.

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