ORIGINAL CLINICAL SCIENCE

Impact of pre-operative coronary artery disease on cardiovascular events following lung transplantation

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BACKGROUND: This study examined the correlation between pre-operative coronary artery disease (CAD) and post-operative cardiovascular events in lung transplant recipients.
METHODS: Consecutive isolated lung transplant recipients from 2007 to 2013 in our institution were identified and categorized as having significant CAD ($\geq$ 50% coronary stenosis in at least 1 artery or history of coronary revascularization) or no–mild CAD. Patient records and death index data were analyzed for a median of 2 years for death or cardiovascular events, including coronary, cerebrovascular, and peripheral artery events.
RESULTS: The study comprised 280 patients (62% male) with mean age of 60 $\pm$ 10 years. Cardiovascular events occurred in 5.7% (16 of 280) of the entire cohort. Patients with significant CAD had a higher annualized rate of cardiovascular events than those with no–mild CAD (11.9% vs 0.6%; $p < 0.001$). Significant CAD was an independent predictor of cardiovascular events (hazard ratio, 20.32; 95% confidence interval, 5.79–71.26; $p < 0.001$) but not all-cause mortality (log-rank $p = 0.66$). Adding significant CAD to clinical risk factors gave incremental prognostic performance compared with clinical risk factors alone ($p < 0.001$ for increase in global chi-square).
CONCLUSION: Selected lung transplant candidates with significant CAD can undergo transplantation with equal mortality risk to those without CAD but are at a higher risk of non-fatal cardiovascular events. These data support the current practice of accepting a selected group of patients with CAD for lung transplantation and suggest that they should be monitored early and treated to prevent cardiovascular complications.
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Atherosclerosis is a systemic progressive disease manifesting primarily as coronary artery disease (CAD), cerebrovascular disease, and peripheral artery disease (PAD). It can potentially lead to death and major morbidity if not treated early medically (e.g., aspirin, statins) or procedurally. In lung transplant recipients, atherosclerosis is not uncommon,[1] and immunosuppression can theoretically contribute to further progression of atherosclerosis. Because immunosuppressive therapy can potentially accelerate atherosclerotic diseases and leads to adverse events,[2,3] it is important to understand the outcomes of patients with CAD who undergo lung transplantation, especially in the first 5 to 6 years post-operatively.[4]

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Coronary angiography is considered a gold standard diagnostic tool to evaluate CAD. In our program, coronary angiography is performed pre-operatively in lung transplant candidates aged ≥ 40 years. The presence of CAD, whether treated by interventional techniques or surgery, is not an absolute contraindication for lung transplantation.[5] Specifically, selected patients with CAD and no or minimal evidence of residual ischemia are selected for lung transplantation. These patients may be at a higher risk of cardiovascular events than those without CAD. To date, literature demonstrating the effect of varying degrees of CAD on atherothrombotic vascular events outside the perioperative period in the lung transplant population is limited.[6–8] Accordingly, the aim of this study was to examine the prognostic effect of pre-operative CAD of lung transplant recipients on death and cardiovascular events.

Materials and methods

The Houston Methodist Hospital Institutional Review Board approved this study.

Study design and patient selection

This was a retrospective observational study of consecutive patients who underwent isolated lung transplantation between June 2007 and February 2013 at Houston Methodist Hospital. A total of 324 isolated lung transplantation were identified. According to our institution policy, CAD without symptoms of myocardial ischemia is not an exclusion criterion for lung transplantation. All lung transplant candidates aged > 40 years with at least 1 traditional risk factor for CAD (history of hypertension, diabetes mellitus, dyslipidemia, or smoking) are required to have coronary evaluation using coronary angiography by left-heart catheterization before the transplant. Patients without available coronary angiographic data on record were excluded ($n = 44$). Of the excluded patients, 33 did not meet the criteria (no cardiovascular events occurred) and 11 patients met the criteria but without available angiographic data on record (one stroke occurred). The final cohort comprised 280 patients. A flow chart of patient inclusion is shown in Supplement 1 (available on the jhltonline.org Web site).

Data collection and clinical characteristics

Patient pre-operative demographics, operative data, post-operative clinical features, and clinical events during the follow-up period were collected through our medical record database and lung transplantation registry database, which included lung transplantation procedure data and all follow-up clinic visits as well as other outpatient documents. We categorized primary lung pathology according to the United Network for Organ Sharing classification of lung diseases. Group A is obstructive lung diseases (e.g., emphysema). Group B is pulmonary vascular diseases (e.g., primary pulmonary hypertension). Group C is cystic fibrosis or other immunodeficiency disorders. Group D is restrictive lung diseases (e.g., idiopathic pulmonary fibrosis).

Significant CAD was determined as history of prior coronary revascularization (percutaneous coronary intervention (PCI) or coronary artery bypass graft [CABG] surgery) or sub-clinical coronary stenosis of ≥ 50% of the lumen detected by pre-transplant coronary angiography. Mild CAD was defined as the presence of coronary stenosis of ≤ 50% without prior coronary revascularization. The interval between coronary angiography and lung transplantation was calculated from the date of the left-heart catheterization procedure to the transplant date. Given the evidence showing acceptable clinical outcomes in lung transplant recipients with sub-clinical CAD irrespective of pre-operative coronary revascularization,[9–13] none of our patients with sub-clinical CAD underwent coronary revascularization before or at the same time as lung transplant.

Study outcomes

Clinical events were examined by searching through the medical record database, lung transplantation registry records, and the Social Security Death Index. The outcomes evaluated in this study were post-operative length of stay, death, and atherothrombotic vascular events, including coronary events, cerebrovascular events, and PAD events.

The primary study outcome in our study was the first occurrence of any cardiovascular events. This was defined as a composite outcome of coronary events, carotid events, and PAD events. Coronary events were determined as PCI, CABG, or nonfatal myocardial infarction (MI). Cerebrovascular or carotid events included ischemic stroke and transient ischemic attack (TIA). PAD events were defined as symptomatic abdominal aortic aneurysm, peripheral artery revascularization, or limb ischemia with gangrene. Time to event was calculated from the date of lung transplantation to the date of the event.

The secondary outcomes were death and post-operative length of stay. Death was from all causes and included death after lung transplantation at any time interval. Time to death was counted from the date of the transplantation to the date of death. Post-operative length of stay was calculated from the date of lung transplantation to the date of hospital discharge.

Statistical analysis

For the examination of risk factors for sub-clinical coronary stenosis ≥ 50%, only the patients without prior coronary revascularization ($n = 257$) were included in the analysis. Univariable logistic regression analysis was performed. Pre-operative clinical variables with a univariable p-value of < 0.10 were then included in the multivariable logistic regression model for adjustment.

To identify prognostic effect of significant pre-operative CAD on death and atherothrombotic vascular events, cumulative survival as a function of time was investigated using Kaplan-Meier analysis. Differences in survival and freedom from vascular events among patients with and without significant CAD were compared using log-rank tests. The influence of significant CAD on event-free survival was assessed with univariable Cox regression analysis. All potential independent predictors with a p-value of < 0.10 in univariable analysis were included into multivariable Cox regression models. The regression analysis results are presented as odd ratios (OR) and hazard ratios (HR) and the 95% confidence interval (CI).

Performances of different models for the prediction of post-transplant vascular events using pre-operative clinical characteristics and pre-operative clinical characteristics plus presence of significant pre-operative CAD were evaluated by comparison of the global chi-square score of each predictive model using analysis of variance F test. Function for each predictive model was built