Long-term survival in lung transplant recipients after successful preoperative coronary revascularization

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Objective: Coronary artery disease is considered a contraindication to lung transplantation. We studied effect of pre-lung transplantation nonobstructive coronary artery disease and revascularized coronary artery disease on long-term lung transplant survival.

Methods: Clinical courses of 172 lung transplant recipients from December 1990 to May 2003 were reviewed. Significant coronary artery disease, defined as left main stenosis of greater than 50% or other epicardial vessel stenosis of greater than 70%, was present in 7 patients; 6 received percutaneous coronary intervention and 1 received coronary artery bypass grafting before transplantation.

Results: Groups were similar with regard to sex, race, or length of intensive care days. The group with normal coronary arteries was significantly younger than the groups with coronary artery disease. The revascularized group had a significant increase in dysrhythmias ($P < .003$) and 1-, 3-, and 5-year survivals of 85%, 85%, and 69%, respectively. Those with insignificant coronary artery disease (14 patients) demonstrated a 1-, 3-, and 5-year survival of 64%, 40%, and 32%, respectively. The normal coronary group (151 patients) had a 1-, 3-, and 5-year survival of 75%, 58%, and 40%, respectively. The revascularized group had a significant survival advantage compared with that of the insignificant coronary artery disease group ($P < .04$, log-rank test).

Conclusion: Long-term survival of lung transplant recipients with revascularized coronary arteries is similar to that of subjects with normal coronary arteries, despite an increased incidence of dysrhythmias. Lung transplant recipients with insignificant coronary artery disease had a worse survival than the revascularized group. More studies are needed to ascertain the cause and determine the optimal management for lung transplant recipients with insignificant coronary artery disease.

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Significant coronary artery disease (CAD) has traditionally been considered a contraindication to lung transplantation.¹ A recent survey of North American lung transplantation centers demonstrated that most programs still considered CAD an absolute or relative contraindication for lung transplantation.² Because of shared risk factors between chronic lung disease and CAD, patients considered for lung transplantation often have concurrent CAD.³⁻⁵ Snell and colleagues⁵ have reported a CAD prevalence of 17% among patients older than 50 years who received an angiogram during their workup for lung transplantation. The dearth of available donor lungs and suspected poor outcomes have led most lung transplantation centers to turn down candidates with CAD for lung transplantation.^{1,2} Data from the International Society for Heart and Lung Transplantation registry demonstrating a 5% annual mortality in lung allograft recipients (LARs) caused by CAD⁶ and evidence that renal allograft recipients have a worse outcome in the setting of preoperative CAD⁷ provide indirect support of this practice habit. Furthermore, there is the concern that chronic immunosuppression, the metabolic consequences of

TABLE 1. Demographics for the 3 lung transplant groups (n = 172)

	Normal CAD	ISCAD	SCAD	P value
No. of patients	151	14	7	
Age (y)*	40 ± 15	57 ± 6	59 ± 6	<.05
Male sex	73 (48%)	8 (57%)	4 (57%)	
SLTX (%)	47 (31%)	10 (71%)	6 (86%)	<.0003
BLTX (%)	104 (69%)	4 (29%)	1 (14%)	
Diagnosis				
Emphysema (%)	36 (24%)	12 (86%)	3 (43%)	<.0001
IPF (%)	25 (17%)	2 (14%)	2 (29%)	
Other (%)	90 (60%)	0	2 (29%)	
Dysrhythmia (%)	27 (18%)	3 (21%)	5 (71%)	<.003

CAD, Coronary artery disease; ISCAD, insignificant coronary artery disease; SCAD, significant coronary artery disease; SLTX, single lung transplantation; BLTX, bilateral lung transplantation; IPF, idiopathic pulmonary fibrosis. *Data are expressed as means ± SD.

the immunosuppressants (ie, diabetes, hypertension, and dyslipidemia), or both may accelerate atherosclerosis.⁸

Several groups have reported case reports or small case series of successful lung transplantation after revascularization either by means of coronary artery bypass grafting (CABG), angioplasty, or angioplasty with stent placement.^{5,9-13} The long-term outcomes of lung transplant recipients with revascularized CAD or the outcomes of lung transplant recipients with insignificant CAD on preoperative evaluation have not been reported. We sought to determine the importance of pre-lung transplantation nonobstructive CAD and the role of revascularization of significant CAD (SCAD) on 5-year survival at our center.

Methods

A retrospective chart review was conducted on the clinical course of all patients who underwent lung transplantation at Ochsner Clinic Foundation between December 1990 and May 2003. All patients were evaluated by using a pretransplantation protocol and had normal left ventricular function. Potential candidates older

than 45 years or candidates younger than 45 years with 2 or more risk factors for coronary artery disease were evaluated with a coronary angiogram. Risk factors were defined as male sex, smoking history, hypertension, diabetes, hypercholesterolemia, angina, or history of CAD in a first-degree relative.¹⁴ Because left-heart catheterization (LHC) is invasive, it was the last test performed in otherwise suitable lung transplantation candidates. LHC was performed through the standard percutaneous femoral approach, and selective angiography was undertaken with multiple cineangiographic views. A significant coronary lesion was defined as a stenosis of greater than 50% of the left main coronary artery or greater than 70% of any other epicardial vessel. The insignificant coronary artery disease cohort (ISCAD) was defined as any stenosis not meeting significant criteria. Patients with ISCAD received antihypertensive therapy with angiotensin receptor blockers and hypercholesterol therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors when indicated. Normal LHC was defined as no visualized stenosis. All coronary angiograms were read by the same cardiothoracic surgeon.

Those patients with significant coronary lesions underwent revascularization through percutaneous transluminal angioplasty with stent placement in all amendable lesions before transplantation or CABG before transplantation. The continued patency of arteries subjected to stenting was aided by antiplatelet therapy (aspirin for life and clopidogrel for 3 months). In addition, patients with SCAD received antihypertensive therapy with angiotensin receptor blockers and hypercholesterol therapy with HMG-CoA reductase inhibitors when indicated.

Continuous data were analyzed by using analysis of variance, and categorical data were evaluated by using the Fisher exact test or χ^2 test, whichever was appropriate. All tests were 2 tailed. Survival curves were constructed with the Kaplan-Meier method and compared by using log-rank tests. All statistics were performed with SAS version 7.0 software.

Results

One hundred seventy-two patients underwent transplantation between 1990 and May 2003 at the Ochsner Clinic Foundation. Ninety-nine patients met the criteria for LHC. Of the 73 patients who did not receive LHC, 62 had cystic fibrosis. The remaining 11 patients without cystic fibrosis

TABLE 2. Outcomes for patients with significant coronary artery disease who underwent revascularization

Patient no.	Coronary artery lesion	Intervention	Type of LT/CPB	Outcome (d)	Cause of death
1	95% RCA	Stent	LSLTX/no	2239/deceased	BOS
2	80% MID LAD	Stent	LSLTX/no	1249/deceased	BOS
3	95% MID LAD	Stent	LSLTX/no	2296/deceased	BOS
4	100% LAD, 60% D1	CABG	RSLTX/yes	14/deceased	Dysrhythmia
5	100% RCA	Stent	RSLTX/no	1342/alive	
6	90% OMB, 50% D1	Stent	LSLTX/no	2893/alive	
7	100% RCA, 30% LAD, 20% CX	Stent	BSLTX/no	1095/alive	

LT, Lung transplantation; CPB, cardiopulmonary bypass; RCA, right coronary artery; LSLTX, left single lung transplantation; BOS, bronchiolitis obliterans syndrome; LAD, left anterior descending artery; D1, first diagonal branch; CABG, coronary artery bypass graft; RSLTX, right single lung transplantation; OMB, obtuse marginal branch; CX, circumflex coronary artery; BSLTX, bilateral sequential lung transplantation.

TABLE 3. Survival for all groups of patients who underwent revascularization

Survival	Normal CAD (%)	ISCAD (%)	SCAD (%)
1 y	75	64	85
3 y	58	40	85
5 y	40	32	69

CAD, Coronary artery disease; ISCAD, insignificant coronary artery disease; SCAD, significant coronary artery disease.

were younger than 40 years. Of those who received LHC, 14 LARs were found to have ISCAD, and 7 had SCAD. The demographics among the groups are shown in Table 1. As expected, LARs without CAD comprised a significantly younger cohort.

Six LARs were treated with percutaneous transluminal coronary angioplasty with stent placement before transplantation and 1 patient underwent single-vessel CABG before transplantation. The outcomes of the 7 patients receiving revascularization are detailed in Table 2. Table 3 shows survival at 1, 3, and 5 years for all 3 groups. Survival in the SCAD group was significantly better than that in the ISCAD group ($P < .04$, log-rank test; Figure 1). The mean survival among the 3 groups was 3.9 ± 0.25 years for those with

TABLE 4. Causes of death within the first year after transplantation

	NCAD (n = 151)	ISCAD (n = 14)	SCAD (n = 7)
Acute graft failure	4	2	0
Infection	19	2	0
Technical	7	0	0
Multisystem organ failure	3	0	0
Acute coronary syndrome	0	1	0
Dysrhythmia	0	0	1

P = not significant. NCAD, Normal cardiac arteries; ISCAD, insignificant coronary artery disease; SCAD, significant coronary artery disease.

normal cardiac arteries (NCAD), 3.0 ± 0.7 years for those with ISCAD, and 5.3 ± 1 years for those with SCAD. Table 4 shows the cause of death among the different cohorts. Most of the deaths in the ISCAD group occurred within the first year. One of these deaths was due to an acute coronary syndrome. Bronchiolitis obliterans syndrome was the leading cause of late death in all groups (Table 5). The treatment rates for hypertension and diabetes mellitus were not different among the 3 cohorts (Table 6). In addition, the use of statins did not significantly differ among the groups.

Discussion

CAD is often found among candidates for lung transplantation.³⁻⁵ The majority of centers still consider CAD to be a relative or absolute contraindication for lung transplantation.² There have been a few reports of successful cases of CABG immediately before lung transplantation with successful outcomes.^{12,13} Several case reports and series have demonstrated revascularization with CABG at the time of transplantation or with pretransplantation percutaneous coronary intervention, resulting in successful lung transplant outcomes.^{5,9-11} However, no one has reported long-term outcomes. Our study adds to the previous series of successful lung transplantations in patients with CAD amenable to revascularization. In addition, we demonstrate that 5-year

Figure 1. Overall survival for lung transplant recipients with normal coronary arteries (NCAD), insignificant coronary artery disease (ISCAD), or revascularized significant coronary artery disease (SCAD).

TABLE 5. Causes of death greater than a year after transplantation

	NCAD (n = 151)	ISCAD (n = 14)	SCAD (n = 7)
Bronchiolitis obliterans syndrome	34	3	3
Infection	14	1	0
Acute renal failure	1	0	0

P = not significant. NCAD, Normal cardiac arteries; ISCAD, insignificant coronary artery disease; SCAD, significant coronary artery disease.

TABLE 6. Management of cardiovascular related comorbidities

	NCAD (n = 151)		ISCAD (n = 14)		SCAD (n = 7)	
	Pre-Tx	Post-Tx	Pre-Tx	Post-Tx	Pre-Tx	Post-Tx
Hypertension	17	97	2	9	2	6
Diabetes mellitus	12	60	0	3	0	1
Hyperlipidemia*	0	48	3	6	2	4

P = not significant. NCAD, normal cardiac arteries; ISCAD, insignificant coronary artery disease; SCAD, significant coronary artery disease. *Statin treated.

survival rates are consistent with LARs without CAD at our center.

There are no data on the long-term survival of LARs after coronary revascularization. Our data demonstrate that long-term survival among the SCAD group is comparable with that of LARs with normal coronary arteries, despite the former consisting of an older cohort and more single-lung transplantations and being associated with more dysrhythmias. Interestingly, we found worse outcomes among the LARs with ISCAD. The worse outcomes for LARs with ISCAD suggest that these coronary lesions might pose a problem after lung transplantation. One explanation is that the immunosuppressants themselves, the metabolic consequences of the immunosuppressants (eg, diabetes mellitus, hypertension, and hypercholesterolemia), or both might accelerate atherosclerotic vascular disease after transplantation. However, most of the deaths in the ISCAD group occurred early within the first year. These early deaths might have occurred by chance because of the small number of cases. However, we cannot rule out the possibility of these early deaths being related to these presumed insignificant coronary lesions. Further studies are needed to elucidate whether there is a true association between ISCAD and worse outcomes after lung transplantation.

Our study is limited by its retrospective design. In addition, it is a single-center study consisting of few subjects in 2 of the cohorts. However, these favorable short-term outcomes are consistent with previously published series. Repeated favorable long-term outcomes observed by other groups would confirm the utility of CAD revascularization for lung transplantation candidates with correctable CAD.

In conclusion, coronary revascularization for SCAD might allow individuals with correctable CAD to safely

undergo lung transplantation and have successful long-term outcomes. The optimal method of revascularization depends on the expertise of the institution. ISCAD might not be so insignificant for LARs. Further studies are needed to elucidate the reasons for these worse outcomes and to improve the medical management.

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