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Prevalence of Obstructive Coronary Artery Disease in Patients Undergoing Lung Transplantation: Case Series and Review of the Literature

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Abstract

Background—Coronary angiography is commonly performed prior to lung transplantation, but its utility is unproven.

Methods—We conducted a single-center retrospective analysis of consecutive patients referred for coronary angiography as part of a pre-operative evaluation for lung transplantation and reviewed the literature for prior series.

Results—A total of 89 patients, 48 men and 41 women were included. Obstructive (> 70% stenosis) CAD was present in 9 (10%), non-obstructive (< 70% stenosis) CAD in 24 (27%), and no angiographic evidence of CAD in 56 (63%) patients. We found 13 previously published series in the literature, in which a total of 1998 patients underwent coronary angiography pre-lung transplant. Together with our 89 patients, obstructive CAD was found in 11%.

Conclusions—In conclusion, given the low prevalence of obstructive CAD in patients referred for lung transplantation, the inherent risk of angiography and unproven benefit of detection of obstructive CAD, the utility of routine coronary angiography in this population requires validation in prospective studies.

Keywords

CAD prevalence; lung transplantation

Background

The presence and severity of coronary artery disease (CAD) impacts the selection of patients referred for lung transplantation: obstructive CAD (defined as luminal diameter stenosis of 70%)¹ not amenable to percutaneous or surgical revascularization is a relative

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contraindication to lung transplantation at most centers. Practice guidelines regarding preoperative assessment of CAD have been published for the evaluation of liver and kidney transplant candidates, but not for lung transplantation.² Although protocols vary across institutions, coronary angiography is commonly performed in lung transplant candidates. The prevalence of CAD in this population varies widely in published reports due, at least in part, to different definitions of significant CAD: Many studies defined angiographic CAD as luminal stenosis $\geq 50\%$, however, lesions $\geq 70\%$ are considered flow-limiting and potential targets for revascularization.¹ Moreover, the contentions that (a) CAD on preoperative angiography predicts postoperative cardiac complications, and (b) coronary revascularization prior to non-cardiac surgery improves clinical outcomes, were disproven in a large randomized controlled trial of high-risk population undergoing major vascular surgery.³ Thus, in the absence of prospective clinical trials, whether the benefit of routine preoperative coronary angiography and revascularization outweighs its risks in the pre-lung transplant population is unknown. Since the prevalence of obstructive CAD in this population is an important part of this risk-benefit analysis, we performed a retrospective analysis of patients who underwent coronary angiography as part of the preoperative work-up for lung transplantation in our institution and summarized the published series in the literature.

Methods

After approval from the Investigational Review Board we conducted a single-center retrospective analysis of consecutive patients without known history of CAD referred for coronary angiography as part of a preoperative evaluation for lung transplantation from January 1, 2006 to January 31, 2012. We collected baseline demographic and clinical information including co-morbidities, medications, laboratory values, 12-lead electrocardiogram findings, echocardiographic information, hemodynamic data, coronary angiogram findings and long-term clinical outcomes. The data were obtained from the electronic medical record and the cardiac catheterization laboratory database. Obstructive CAD was defined as $\geq 70\%$ luminal narrowing of a major epicardial coronary artery, or $\geq 50\%$ luminal narrowing of the left main coronary artery, and non-obstructive CAD was defined as $< 70\%$ luminal narrowing of a major epicardial coronary artery.¹

We searched the published research for reported case series of preoperative coronary angiography as part of the pre-lung transplant work-up. We reviewed the MEDLINE database (National Library of Medicine, Bethesda, Maryland) for reports published from 1990 to 2013. The following key words were used in the search: “coronary revascularization”, “coronary intervention”, “coronary angiography”, “stent”, “cardiac catheterization”, “preoperative”, “lung transplant”, “lung transplantation”, “coronary artery disease”, “CAD”, and “prevalence”. The search was limited to articles written in English and only primary reports of series were included in the review. Post-operative myocardial infarction was defined according to the Third Universal Definition of Myocardial Infarction.⁴

Statistical Analysis

Results are presented as mean values $\pm$ standard deviation for continuous data and relative frequency (percentages) for categorical data. Chi-squared analysis was used to analyze categorical data and ANOVA was used to analyze continuous data between patient groups.

Results

A total of 89 patients underwent coronary angiography at our institution as part of their preoperative work-up for lung transplantation between January 1, 2006 and January 31, 2012. The mean pre-transplant age of the 48 men and 41 women was 56 ± 7 years (range, 37–69 years). The majority had chronic obstructive lung disease or interstitial lung disease as the indication for lung transplantation (Table 1). Obstructive CAD was present in 9 (10%), non-obstructive CAD in 24 (27%), and no angiographic evidence of CAD was found in 56 (63%). No patients were referred for stress testing at our institution prior to coronary angiography.

Patients with obstructive CAD had significantly higher rates of hypercholesterolemia (73% vs. 34% vs. 54%, $p=0.028$) and hypertension (44% vs. 21% vs. 4%, $p=0.044$) compared to patients with either no CAD or non-obstructive CAD, but the rates of diabetes, prior smoking, and family history of CAD did not differ between groups (Table 1). When assessed according to the aggregate number of cardiac risk factors, patients with obstructive CAD were more likely to have ≥ 3 cardiac risk factors compared to those with non-obstructive CAD and no CAD (67% vs. 38% vs. 20%, $p=0.009$). On electrocardiography, non-specific ST segment changes and T wave inversions were present in 13% of the patients, with a similar frequency across the groups. Moreover, there was no difference in right heart pressure measurements or left ventricular systolic function as assessed by left ventriculography between groups.

A total of 38 patients (43%) underwent lung transplantation (Table 2). Of the 9 patients with obstructive CAD (7 with single vessel disease and 2 with two vessel disease, no patient had significant left main disease), 6 underwent percutaneous revascularization at the time of the index angiogram (5 with placement of bare metal stents, and 1 with a drug-eluting stent), but only one patient (treated with a bare metal stent) underwent subsequent lung transplantation and this was complicated by a post-operative type II myocardial infarction (peak troponin I level was 6.6 ng/mL). Of the 24 patients with non-obstructive CAD, 11 underwent lung transplantation, 4 sustained type II myocardial infarctions post-operatively, and 2 died of non-cardiac causes (perioperative bleeding and sepsis). Of 56 patients with no angiographic evidence of CAD, 26 underwent transplantation, 7 sustained a type II myocardial infarction post-operatively, and 7 died of non-cardiac causes (rejection, infection or bleeding). Of the 51 patients who did not receive lung transplantation (30 with no CAD, 13 with non-obstructive CAD, and 8 with obstructive CAD), 1 developed atrial fibrillation, 1 sustained a type I myocardial infarction (non-obstructive CAD was found on the index angiogram) and 7 died (all deaths due to respiratory failure and infection) at one year follow-up.

Of the 19 published case series reviewed, 13 fulfilled our search criteria.^{5–17} The remaining reports were not included because the study included only mild ($< 50\%$) stenoses¹⁸, no

angiographic data was provided^{19,20}, and no prevalence data were provided^{21,22,23}. Articles were reviewed by 2 of the investigators (R. M. J. and E. C. K.) and data were tabulated (Table 3). A total of 1998 patients underwent coronary angiography. When restricting the analysis to only those 5 studies that defined CAD as obstructive^{9,11,13,14,17}, and including our own data, the prevalence of obstructive CAD was 11% (Table 4).

Discussion

In our case series of the prevalence of obstructive CAD was low (10%) and consistent with results from prior studies.^{9,11,13,14,17} The variation in the reported prevalence of CAD in patients being considered for lung transplantation is at least in part, due to variable definitions: CAD defined as ≥70% diameter stenosis on coronary angiography is considered flow-limiting.¹ The majority of the reviewed studies used ≥50% luminal diameter stenosis the presence of CAD but did not specify how many patients, if any, had obstructive CAD. When we tabulated the 5 studies that reported the prevalence of obstructive CAD^{9, 11, 13, 14,17} and included our case series, the prevalence of obstructive CAD was 11%.

Despite a much higher prevalence of CAD in patients with end-stage renal disease, current American Heart Association/American College of Cardiology guidelines for preoperative cardiac assessment prior to kidney transplantation recommends beginning with a thorough history and physical to determine if an active cardiac condition exists.² For patients with no active cardiac conditions, non-invasive stress testing may be considered based on the presence of multiple CAD risk factors defined as 3 or more of the following: diabetes mellitus, prior cardiovascular disease, more than one year on dialysis, left ventricular hypertrophy, age > 60 years, smoking, hypertension, and dyslipidemia.² Importantly, there is no recommendation made regarding the use of routine coronary angiography in preoperative testing prior to kidney transplantation. Moreover, the lack of correlation between angiographic CAD and clinical outcomes is highlighted and the routine use of prophylactic coronary revascularization in patients with stable CAD without symptomatic or survival implications is not recommended.²

Given the low pre-test probability of obstructive CAD in the lung transplant population, a non-invasive screening test with high sensitivity but low specificity would prevent unnecessary coronary angiography and its inherent risks, without increasing the portion of subjects with unsuspected obstructive CAD undergoing transplantation. In this context, non-invasive stress-testing is of limited utility in the end-stage lung disease population due to inability to exercise, body habitus limiting imaging, and other technical and physiologic factors.⁶ Cardiac computerized tomography (CT) angiography, however, is a non-invasive technique that accurately rules out obstructive CAD in patients with low or intermediate pre-test probability with good positive (87%) and negative (90%) predictive values, making it a potentially effective screening tool for exclusion of significant stenosis.²⁴ Moreover, the limitations of cardiac CT angiography²⁴, namely extensive coronary calcification and potential for contrast-induced nephrotoxicity, are less applicable to the end-stage lung disease population. The utility of cardiac CT angiography in this setting requires prospective validation. Our case series is limited by the fact that it is a single center, observational study

and includes a relatively small number of patients. However, the summary data from 11 other case series represents the largest aggregate of data on this topic.

Conclusions

Given the low prevalence of obstructive CAD in patients referred for lung transplantation and the inherent risk of angiography, the utility of routine coronary angiography in this population requires validation in prospective studies. Moreover, trials are necessary to determine whether an initial non-invasive screening strategy, such as with cardiac CT angiography, can reduce the number of patients undergoing invasive coronary angiography. More broadly, randomized studies are needed to determine whether the detection and revascularization of obstructive CAD in this population reduces the incidence of peri-operative complications.

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Table 1

Baseline characteristics according to the presence of coronary artery disease

Variable	No CAD N=56	Non-obstructive CAD N=24	Obstructive CAD N=9	P Value
Age (yrs) +/- SD	55 +/- 8	59 +/- 5	59 +/- 7	0.149
Gender				0.299
Men	27 (48%)	14 (58%)	7 (78%)	
Women	29 (52%)	10 (42%)	2 (22%)	
Race				0.874
White	47 (84%)	21 (88%)	8 (89%)	
Black	9 (16%)	3 (13%)	0	
Diagnosis				
1	27 (48%)	9 (38%)	5 (56%)	0.571
2	18 (32%)	12 (50%)	4 (44%)	0.260
3	5 (9%)	1 (4%)	0	
4	3 (6%)	0	0	
5	3 (6%)	2 (8%)	0	
Hypertension	12 (21%)	9 (4%)	4 (44%)	0.044
Diabetes mellitus	8 (15%)	5 (21%)	1 (9%)	0.647
Hypercholesterolemia	19 (34%)	13 (54%)	8 (73%)	0.028
Smoking history	37 (69%)	22 (92%)	8 (73%)	0.089
Family history of CAD	17 (31%)	4 (17%)	3 (27%)	0.396
3 cardiac risk factors	11 (20%)	9 (38%)	6 (67%)	0.009
ST-T wave changes on 12-lead ECG	5 (9%)	3 (13%)	1 (11%)	0.884
Wall motion abnormalities on TTE	5 (9%)	2 (8%)	0	--
Systolic blood pressure (mmHg)	126 +/- 17	128 +/- 19	130 +/- 19	0.573
Diastolic blood pressure (mmHg)	76 +/- 12	81 +/- 12	76 +/- 12	0.205
Heart rate (bpm)	82 +/- 12	83 +/- 14	87 +/- 14	0.664
Left ventricular ejection fraction (%)	61 +/- 7	61 +/- 8	61 +/- 8	0.940
Right atrial pressure (mmHg)	8 +/- 4	8 +/- 4	7 +/- 4	0.777
Right ventricular systolic pressure (mmHg)	45 +/- 17	41 +/- 10	46 +/- 12	0.408
Pulmonary artery systolic pressure (mmHg)	30 +/- 12	30 +/- 11	34 +/- 10	0.280
Pulmonary capillary wedge pressure (mmHg)	12 +/- 5	11 +/- 5	11 +/- 5	0.367

Data are presented as absolute number (%), mean +/- SD, CAD=coronary artery disease, ECG= electrocardiogram, TTE= transthoracic echocardiogram, Diagnoses (1= COPD/emphysema/alpha-1-antitrypsin; 2= Interstitial lung disease/Idiopathic pulmonary fibrosis/Pulmonary fibrosis; 3= Sarcoidosis; 4= Cystic fibrosis/bronchiectasis; 5= Coal Worker's Pneumoconiosis).

Table 2

One-year cardiovascular outcomes

Variable	No CAD N=26	Non-obstructive CAD N=11	Obstructive CAD N=1
Lung transplant			
Congestive heart failure	0	1	0
Post-operative MI	7	4	1
Atrial fibrillation	0	1	0
Death	7	2	0
Non-cardiac death	7	2	0
Incidence of major adverse cardiac outcomes*	7/26 (27%)	6/11 (55%)	1/1 (100%)
No lung transplant			
Congestive heart failure	0	0	0
MI	0	1	0
Atrial fibrillation	1	0	0
Death	3	3	1
Non-cardiac death	3	3	1
Incidence of major adverse cardiac outcomes*	1/30 (3%)	1/13 (8%)	0 (0%)

CAD= coronary artery disease; MI= myocardial infarction; data are presented as absolute number (%), mean $\pm$ SD * major adverse cardiac outcomes = combination of congestive heart failure, MI, atrial fibrillation and cardiac death.

Table 3

Clinical features and coronary angiographic data of patients referred for preoperative coronary angiography prior to lung transplantation as reported in the literature

Reference	Total number (number who underwent coronary angiography)	Men/Women	Age (years) mean $\pm$ SD	Smoking	Hypertension	Diabetes	Hyperlipidemia	Family history of CAD	CAD identified
5	77	33/44	55 $\pm$ 7	77 (100%)	7 (9%)	5 (7%)	8 (10%)	2 (3%)	9 (12%)*
6	23 (19)	15/8	48 $\pm$ 12	NR	NR	NR	NR	NR	4 (21%)*
7	105 (51)	45/60	43 $\pm$ 4 (range 18–63)	55 (52%)	12 (11%)	4 (4%)	27 (26%)	18 (17%)	3 (6%)*
8	101 (85)	56/45	All patients 50	83 (82%)	22 (22%)	4 (4%)	48 (48%)	NR	16 (19%)*
9	120 (74)	55/65	48 $\pm$ 13 (transplanted) 45 $\pm$ 15 (listed)	49 (41%)	29 (24%)	12 (10%)	41 (34%)	NR	17 (23%)§
10	169 (38)	34/4	57 (range 42–66)	33 (87%)	6 (16%)	5 (13%)	7 (19%)	NR	6 (16%)*
11	354 (256)	NR	57 $\pm$ 9 (range 38–67)	NR	NR	NR	NR	NR	18 (7%)*
12	630	287/343	51 (range 27–65) (fibrotic) 54 (range 19–66) (nonfibrotic)	10 pack-years (range 0–111) 40 pack-years (range 0–200)	152 (24%)	50 (8%)	216 (34%)	190 (30%)	70 (11%)*
13	118	80/38	58 (range 53–61)	85 (72%)	38 (32%)	29 (25%)	25 (21%)	NR	21 (18%)*
14	172 (99)	85/87	40 $\pm$ 15 (no CAD) 57 $\pm$ 6 (non-obstructive CAD) 59 $\pm$ 6 (obstructive CAD)	NR	21 (12%)	12 (7%)	5 (3%)	NR	7 (7%)*
15	100	69/31	59 $\pm$ 6 (emphysema) 56 $\pm$ 6 (fibrosis)	65 (65%)	17 (17%)	21 (21%)	30 (30%)	NR	19 (19%)*
16	129	81/48	60 $\pm$ 6 (fibrotic) 60 $\pm$ 6 (nonfibrotic)	NR	NR	NR	NR	NR	30 (23%)*
17	473 (322)	155/167	59 (range 54–64)	40 pack-years (range 23–66)	171 (53%)	77 (24%)	106 (33%)	NR	52 (16%)*
Present series	89	48/41	56 $\pm$ 7 (range 37–69)	67 (75%)	25 (28%)	14 (16%)	40 (45%)	24 (27%)	9 (10%)*

Data are presented as absolute number (%), mean $\pm$ SD

* = diameter stenosis 50% in a major epicardial coronary artery

† = diameter stenosis 70% in a major epicardial coronary artery, or 50% narrowing of the left main coronary artery

‡ = diameter stenosis 75% in a major epicardial coronary artery, or 50% narrowing of the left main coronary artery

§ = diameter stenosis provided for each patient: < 50% diameter stenosis (n=1), 50% diameter stenosis (n=3), 70% diameter stenosis (n=3)
NR= not reported

Table 4

Prevalence of obstructive CAD in lung transplant candidates

Reference	Obstructive CAD
9	3/74 (4%)
11	18/256 (7%)
13	21/118 (18%)
14	7/99 (7%)
17	52/322 (16%)
Present series	9/89 (10%)
Summary	110/958 (11%)

Data are presented as absolute number (%), CAD= coronary artery disease