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# The prevalence of coronary artery disease in end-stage pulmonary disease: Is pulmonary fibrosis a risk factor?

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Received 1 May 2008; accepted 18 March 2009

Available online 11 April 2009

## KEYWORDS

Atherosclerosis;  
Coronary angiography;  
Smoking;  
Lung disease;  
Inflammation

## Summary

**Background:** It has been suggested that coronary artery disease (CAD) is a common complicating condition in pulmonary fibrosis.

**Objective:** To establish and compare the incidence of coronary artery disease in lung-transplantation candidates with emphysema and lung fibrosis

**Method:** All adult patients (age > 40 years old) with emphysema or lung fibrosis, candidates for lung transplantation between January 1997 and December 2003, were included. All patients underwent pretransplant coronary angiography.

**Results:** A total of 100 patients were enrolled; 51 with emphysema and 49 with fibrosis. CAD (at least one 50% stenotic coronary artery) was diagnosed in fourteen of 49 (28.6%) patients with lung fibrosis as compared to five out of 51 (9.8%) with emphysema, [ $p = 0.019$ ] despite the fact that 98% of patients with emphysema but only 31% of the patients with lung fibrosis were heavy smokers. The groups didn't significantly differ in any other cardiovascular risks.

**Conclusions:** There is significantly more CAD in lung-transplantation candidates with lung fibrosis as compared to those with emphysema, despite the fact that smoking was much more

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prevalent in the emphysema patients. These results suggest that the inflammatory process in lung fibrosis may involve the coronary arteries as a part of a systemic inflammation rather than an idiopathic fibrotic disease confined to the lungs.

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## Introduction

Lung transplantation is now accepted therapy for diseases that cause end-stage pulmonary disability,<sup>1</sup> principally emphysema and pulmonary fibrosis.<sup>2</sup> Coronary artery disease (CAD) was previously considered an absolute contraindication for lung transplantation, based on the shortage of organs for transplantation, the need to select the best possible candidates, and the potential negative impact of CAD on the morbidity and mortality during and after lung transplantation. However, improvements in management of CAD have removed it from the list of contraindications for lung transplantation.<sup>3</sup> Nonetheless, CAD remains an important potential complicating factor for patients being considered for transplantation.

Recently, Kizer et al. showed an association between CAD and pulmonary fibrosis.<sup>4</sup> Among 186 patients being considered for lung transplantation, the prevalence of CAD (15.9%) was significantly higher than its prevalence among the 444 non-fibrotic patients (10.6%), most but not all of whom had COPD. We undertook this study to confirm Kizer's findings in a different population of patients and to make a direct comparison between lung-transplantation candidates with emphysema and those with pulmonary fibrosis.

## Patients and methods

All adult patients with emphysema or pulmonary fibrosis, candidates for lung transplantation in our institution between January 1997 and December 2003, were included in this study. Emphysema was diagnosed by pulmonary function tests and chest-X-ray radiography or chest CT-scan, according to the ATS/ERS position paper.<sup>5</sup> The diagnosis of pulmonary fibrosis was established according to the ATS statement on idiopathic interstitial pneumonias.<sup>6</sup>

Each patient was evaluated for the presence of following cardiovascular risk factors: hypertension, hypercholesterolemia, diabetes mellitus, obesity, and smoking status. In addition, treatment with glucocorticosteroids during the study was recorded. Hypertension was defined as arterial blood pressure  $\geq 140/90$  mm Hg or treatment with one or more antihypertensive agents. Hypercholesterolemia was defined as total blood cholesterol level of  $\geq 240$  mg/dl or treatment with one or more lipid-lowering drug. Diabetes mellitus was defined as a fasting serum glucose level  $\geq 126$  mg/dl or treatment with one or more oral or parenteral hypoglycemic medications. Obesity was defined as a body mass index, BMI  $\geq 27.0$ .

Significant CAD was defined by  $\geq 50\%$  stenosis of one or more coronary arteries, as reported in the coronary angiography report reviewed for each patient. Non-clinically significant CAD was defined  $\geq 20\%$  to  $<50\%$  stenosis. Absence of CAD was defined as either the absence of stenosis or a stenosis of  $<20\%$ .

## Statistics

In order to compare the different parameters between both groups the two-sided Fisher's exact test was used.  $p < 0.05$  was considered significant.

Hierarchical logistic regression was conducted in order to test the relationship between the diagnosis and CAD while controlling possible confounding factors.

## Results

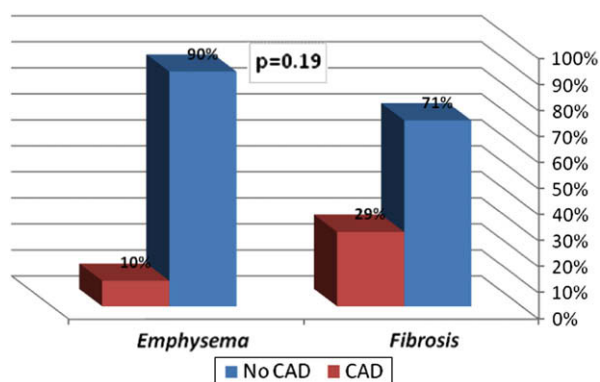
A total of 100 patients were enrolled in this study; 51 with emphysema and 49 with pulmonary fibrosis. Demographic characteristics are shown in Table 1. There was no significant difference in the age and gender between both groups.

Almost all patients with emphysema (98%) were smokers, in comparison to only 30.6% in the fibrosis group ( $p < 0.0001$ ) (Table 1). All patients in the fibrosis group (100%) had been treated with corticosteroids, but only 66.6% in the emphysema group ( $p < 0.0001$ ). There was a trend toward higher prevalence of hypercholesterolemia among patients with emphysema (37.2%) as compared to fibrotic patients (22.4%,  $p = 0.129$ ), but without reaching statistical significance. There was no significant difference in the other cardiovascular risk factors.

Multivariate analysis was done in order to test for possible confounding factors. Fourteen of 49 patients (28.6%) with pulmonary fibrosis as compared to five out of 51 (9.8%) with emphysema had significant CAD ( $\chi^2(1) = 4.57$ ,  $p = 0.019$ ) (Fig. 1) when hierarchical logistic regression was done. Only the differences in single-vessel disease reached statistical significance. Two of the emphysema patients and 4 of the fibrotic patients had been

**Table 1** Demographic characteristics, cardiovascular risk factors and coronary artery disease among lung-transplantation candidates, stratified by diagnosis. Results are expressed as number of patients in each group. NS = non-significant ( $p > 0.05$ ).

	Emphysema	Fibrosis	p-Value
<i>n</i>	51	49	
Age (mean $\pm$ SD) years	58.9 $\pm$ 5.6	55.8 $\pm$ 6.0	NS
Sex (male/female)	35/16	34/15	NS
Corticosteroid therapy	34	49	$<0.0001$
Smoking	50	15	$<0.0001$
Hypertension	10	7	NS
Diabetes mellitus	11	10	NS
Hypercholesterolemia	19	11	NS
Obesity	9	16	NS
Coronary artery disease	5	14	0.019



**Figure 1** Prevalence of CAD among emphysema and pulmonary fibrosis patients referred for evaluation for lung transplantation. Significant CAD (at least one vessel with at least 50% stenosis) was threefold greater among fibrosis than emphysema patients despite the higher prevalence of smoking among the emphysema patients (98% vs. 31% for fibrosis). The absence of CAD (<20% stenosis) was significantly lower in fibrosis patients as compared to emphysema patients.

revascularized, a difference that did not reach statistical significance. No significant difference was found in any other cardiovascular risk between the fibrotic and emphysema groups.

## Discussion

We have shown that coronary artery disease is significantly more prevalent in lung-transplantation candidates with lung fibrosis (28.6%) as compared to those with emphysema (9.8%), despite the fact that far more of the emphysema patients had been cigarette smokers. Moreover, there was no statistically significant difference in the other cardiovascular risk factors between both groups.

The association between pulmonary fibrosis and CAD may be explained by the similarities in their pathogenesis. Fibroblastic proliferation and excessive collagen deposition, whether of lung or coronary arteries, occur either as a direct result of the injury, as a result of anti-inflammatory cell response that releases pro-inflammatory and pro-fibrotic cytokines, or as a consequence of the regenerative and reparative processes taking place at the epithelial and endothelial surfaces.<sup>7,8</sup> Laboratory and pathological data support the idea that inflammation has a role on both the initiation and the progression of atherosclerosis. It has been shown that high level of pro-inflammatory mediators such as interleukin-6, and high-reactivity C-reactive protein were present in patients with coronary artery disease<sup>9</sup> and their presence was predictive of cardiovascular events in patients with stable<sup>10</sup> and unstable angina,<sup>11</sup> as well as in healthy men<sup>12</sup> and women.<sup>13</sup> The active inflammatory process plays a major role in plaque destabilization leading to acute coronary syndrome. Furthermore, some evidence suggests that anti-inflammatory agents may have a role in the prevention of cardiovascular disease.<sup>14</sup> Several lines of evidence also suggest that the fibroproliferative lung process can have systemic effects. Levels of cytokines and growth factors as well as biologically active eicosanoids

have been found to be elevated in the sera or urine of patients with lung fibrosis. Hence, the fibroproliferative process seems to affect cells beyond the pulmonary compartment, and the many mediator molecules produced in these disorders provide multiple potential mechanisms through which they might promote atherogenesis.<sup>4</sup>

Although the pathogenesis of interstitial pulmonary fibrosis has not been fully elucidated, actual concepts focused on lung injury leading to a cycle of chronic alveolar inflammation leading to exaggerated fibroblast proliferation, and excessive deposition of collagen eventuating in fibrosis and destruction of the lung architecture.<sup>15</sup> Interleukin-1 beta and TNF-alpha especially have been shown to increase lung TGF-beta levels, proportionate to the degree of fibrosis generated.<sup>16</sup> Anti-inflammatory therapies employing corticosteroids or immunosuppressive agents alone or as combination therapy have been disappointing.<sup>17</sup>

Our results may suggest that the inflammatory process in pulmonary fibrosis could eventually involve the coronary arteries as a part of a systemic inflammatory disease, rather than an idiopathic disease confined to the lungs. Similarly, it was recently shown that coronary artery atherosclerosis detected by electron-beam CT, is more common in patients with lupus than in the general population but is not associated with traditional coronary risk factors, lupus disease activity, or corticosteroid therapy.<sup>18</sup>

In conclusion, our findings suggest that coronary artery disease is more prevalent among lung-transplantation candidates with pulmonary fibrosis as compared to those with emphysema, despite the fact that emphysema patients have a much greater exposure to cigarette smoking. This tendency to develop significant coronary artery disease among patients with fibrosis as compared to emphysema cannot be predicted by the measurement of traditional risk factors. These results may suggest that the inflammatory process in lung fibrosis could be a systemic disease rather than an idiopathic fibrosis confined to the lungs.

## Conflict of interest

The authors have no conflict of interest.

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