SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2014; 31; 289-296

Association between idiopathic pulmonary fibrosis and coronary artery disease: a case-control study and cohort analysis

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Abstract. *Background:* Although the increased risk of coronary artery disease (CAD) in the patients with idiopathic pulmonary fibrosis (IPF) has been reported, there was few detailed information on the risk factors for CAD in IPF. The aim of this study was to investigate the prevalence of CAD in IPF with analysis of other risk factors. *Methods:* The subjects were 460 patients (mean age, 65 years; 79% male; 74% current or ex-smoker) diagnosed as IPF at Asan Medical Center and 1,925 controls matched with age, gender, smoking habits, and date of IPF diagnosis from the cohort of Korean Heart Study. Cardiovascular risk factors and prevalence of CAD in both groups were compared and the incidence of newly developed CAD during follow-up was also analyzed. *Results:* IPF group was more diabetic, and control group had a higher proportion of hypertension and hypercholesterolemia. The prevalence of CAD in IPF group (7%) was two times higher than that of control group (3%). Multivariate analysis revealed that age (OR, 1.04; 95% CI, 1.02-1.07), hypertension (OR, 2.13; 95% CI, 1.36-3.33), hypercholesterolemia (OR, 3.85; 95% CI, 2.51-5.88), and IPF (OR, 2.64; 95% CI, 1.68-4.14) were significant risk factors for CAD. During follow-up (median: 2.5 years for IPF and 4.4 years for controls), the incidence of newly diagnosed CAD was higher in the patients with IPF (6.8%) compared to controls (2.8%) (RR, 1.92; 95% CI, 1.08-3.43). *Conclusions:* IPF itself was an independent risk factor for CAD after the adjustment of age, hypertension, diabetes, and hypercholesterolemia. *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 289-296)*

Key words: Coronary artery disease, IPF, incidence, risk factors

Received: 26 December 2013
Accepted after revision: 16 April 2014
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Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic lung disease of unknown etiology (1). The incidence of IPF was reported to be increased over recent years (2,3) and the median survival after the diagnosis is about 3 years, yet no treatments have shown to improve survival (4).

There are several studies reporting increased incidence of other diseases such as lung cancer and diabetes, which may have an influence on mortality (5,6). Previous reports suggested a relationship of chronic obstructive pulmonary disease (COPD) with various cardiovascular diseases causing increased risk for hospitalizations and deaths (7-9) and similar association has also been reported in IPF (10-14). Hubbard *et al.* compared the incidence of CAD between IPF and general population, but other risk factors of CAD were not considered. Although several other studies evaluated known cardiovascular risk factors, they were performed in small number of advanced patients without control group.

Therefore the aim of this study was to investigate the risk of CAD in the patients with IPF compared to the general population with detailed analysis of other risk factors at the time of IPF diagnosis and also during follow-up.

Methods

Study design

This was a retrospective analysis of two prospective cohorts, the patients diagnosed as IPF and matched controls. The prevalence and risk factors of CAD in both groups were compared (cross-sectional case-control study) and the incidence of newly developed CAD during follow-up was also evaluated (longitudinal cohort analysis). This study was approved by institutional review board of Asan Medical Center (No. 2010-0334). Written informed consent was waived because it was retrospective observational study.

Subjects

The case group was 460 patients diagnosed as IPF (surgical lung biopsy: 45%) according to ATS/ERS/JRS/ALAT criteria (1) at Asan Medical Center between January, 2004 and December, 2009.

Total 1,925 control subjects (4 controls for one case) matched with age, gender, and smoking habits were selected from the Korean Heart Study cohort, which originally evaluated subjects who had voluntarily undergone private health examinations at 17 centers in six South Korean provinces from 1996 to 2004 (15). In order to match the study period with IPF cases, the cohort period was extended and 254,697 individuals (153,437 men and 101,260 women) between 2004 and 2010 were evaluated. The control subjects were matched with the date of diagnosis of each case. Data regarding newly developed CAD events in controls during follow-up were obtained from the Korean National Health Insurance database.

Data collection and definition

Hospital records and Korean Heart Study records were reviewed to collect the data on the presence of hypertension, diabetes, hypercholesterolemia, and obesity. The definitions used were: hypertension: blood pressure ≥140/90 mmHg, treatment with antihypertensive medication, or history by questionnaire; diabetes: fasting glucose level of 126 mg/dL or greater, use of oral hypoglycemic agents or insulin, or history by questionnaire; hypercholesterolemia: total cholesterol level of 240 mg/dL or higher or use of lipid-lowering therapy; obesity: a body mass index of 25 kg/m^2 or higher.

For the case group, CAD was diagnosed by symptom and the finding of coronary angiography, coronary computed tomography angiography, thallium scan, or exercise treadmill test. For the control group, the International Classification of Diseases, Tenth Revision (ICD-10) codes (I20.0 and I20.8-I20.9 for angina pectoris; I21.0-I21.4 and I21.9 for acute myocardial infarction) were used.

Statistical analysis

Student's *t*-test served to compare continuous data and the chi-square or Fisher's exact test served to compare categorical data. Multiple logistic regression was used to assess factors associated with the prevalence of CAD. To prevent multicollinearity, variables with high correlation between each other

were controlled. The C-statistics was used to assess overall model discrimination. In longitudinal study, CAD incidence during follow-up was obtained by Kaplan-Meier survival curve using CAD as substitute of mortality, and the date of the outcome or last data collection was censored. *P* value less than 0.05 were considered to be significant. All analyses were performed with SAS software version 9.1 (SAS institute, Cary, NC, USA).

Results

Cross-sectional study

The mean age of IPF group at diagnosis was 64.6 ± 8.0 years, 79% were male and 74% were current or ex-smoker (Table 1). Control group had higher prevalence of hypertension and hypercholesterolemia, while diabetes was more prevalent in IPF group.

The prevalence of CAD was two times higher (7%) in IPF group compared to control group (3%) (*P* < 0.001). Among 33 patients with CAD in IPF group, 8 patients (24%) were asymptomatic and CAD was found mostly during IPF work-up (Table 2). Seventeen patients (52%) had angina and remaining 8 (24%) had acute coronary syndrome (ACS). Five patients (15%) had multiple CAD events before the diagnosis of IPF. Most of the diagnosis (85%) was made by coronary angiography. In control group, 74% had angina, 14% had ACS and 12% had multiple events (as both angina and ACS).

The risk factors of CAD were evaluated using logistic regression model (Table 3). Matched variables (age, gender, and smoking habits) were also included. Multivariate analysis revealed that age (OR, 1.04; 95% CI, 1.02-1.07), hypertension (OR, 2.13; 95% CI, 1.36-3.33), and hypercholesterolemia (OR, 3.85; 95% CI, 2.51-5.88) were significant risk factors for CAD. Gender, obesity, and smoking habits

Table 1. Baseline demographic characteristics, cardiovascular risk factors, and coronary artery disease among IPF and control group: cross-sectional case-control study*.

	IPF (n = 460)	Control (n = 1,925)	P
Age (years)	64.6 (±8.0)	63.9 (±8.0)	0.10
Gender (n, % male)	364 (79)	1,508 (78)	0.71
Body mass index (kg/m2)	24.2 (±3.1)	24.2 (±2.7)	0.84
Obesity	179 (39)	730 (38)	0.69
Smoking habits			0.94
Non-smoker	119 (26)	514 (27)	
Ex-smoker	242 (53)	1,001 (52)	
Current smoker	99 (22)	410 (21)	
Hypertension	162 (35)	902 (47)	<0.001
Diabetes	90 (20)	300 (16)	0.04
Hypercholesterolemia†	68 (15)	422 (22)	<0.001
Statin use	52 (11)	166 (9)	0.07
LDL cholesterol (mg/dL)‡			<0.001
<130	264 (73)	1,216 (63)	
130-159	74 (21)	508 (26)	
≥160	22 (6)	201 (10)	
Low HDL cholesterol§, ‖	105 (29)	381 (21)	<0.001
Coronary artery disease	33 (7)	66 (3)	<0.001

IPF, idiopathic pulmonary fibrosis; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
**The data were presented as the number ± standard deviation (SD) or (%) of patients unless indicated otherwise.*
†Hypercholesterolemia: total cholesterol ≥240 mg/dL or statin use.
‡IPF (n = 360) vs. Control (n = 1,925).
§IPF (n = 360) vs. Control (n = 1,838).
‖Low HDL cholesterol: <40 mg/dL for men, <50 mg/dL for women.

Table 2. Coronary artery disease among IPF and control group (before or at the time of IPF diagnosis)

Variable	n (%)
IPF group (n = 33/460)	
Symptomatic	
Angina pectoris	17 (52)
Acute coronary syndrome	8 (24)
Asymptomatic*	8 (24)
Diagnostic method†	
Coronary angiography	28 (85)
Coronary CT angiography	1 (3)
Thallium scan	1 (3)
Exercise treadmill test	2 (6)
ECG change and/or abnormal cardiac enzyme	1 (3)
Control group (n = 66/1,925)	
Angina pectoris	49 (74)
Acute coronary syndrome	9 (14)
Both angina pectoris and acute coronary syndrome‡	8 (12)

IPF, idiopathic pulmonary fibrosis; CT, computed tomography; ECG, electrocardiogram.
**These patients were incidentally diagnosed as CAD, mostly during IPF work-up. All patients had undergone coronary angiography for final diagnosis.*
†If there were more than one method used for CAD diagnosis, only the method used for the final diagnosis was described.
‡For individuals with more than one event, we used just the first event in analysis.

were not important and diabetes was associated with CAD only in univariate analysis. IPF remained as a strong predictor of CAD (OR, 2.64; 95% CI, 1.68-4.14) after the adjustment for other potential confounders. On C-statistics, this model had acceptable discrimination (C-index 0.73).

Incidence of CAD during follow-up

The median follow-up period was 2.5 years for IPF and 4.4 years for controls. The cases with CAD included in the cross-sectional study (n = 99) were excluded. During follow-up period, 17 new CAD events occurred in IPF group and 51 in control group (Table 4). In IPF group, 6 patients (35%) had angina and another 35% had ACS (Table 5). The remaining 5 patients (29%) were asymptomatic and diagnosed by routine health examination. CAD was diagnosed by coronary angiography in 59%. In control group, most of CAD (90%) was angina and only 10% was ACS. The incidence of newly developed CAD was higher in IPF group (6.8%) compared to controls (2.8%). After the adjustment of age, obesity, hypertension, and hypercholesterolemia, the relative risk of newly developed CAD in IPF group was 1.92 (95% CI, 1.08-3.43; $P = 0.03$). Figure 1 shows the cumulative incidence of CAD in two groups.

Outcome of CAD

During follow-up period, 205/460 (45%) died in IPF group and 33/1,925 (2%) in control group. Medical therapy was given to all patients with IPF and

Table 3. Univariate and multivariate analysis of factors associated with coronary artery disease in IPF and control group

Variable	Unadjusted OR (95% CI)	P	Adjusted OR* (95% CI)	P
Age	1.05 (1.02-1.08)	<0.001	1.04 (1.02-1.07)	0.003
Male gender	1.16 (0.70-1.93)	0.57		
Obesity	1.37 (0.91-2.05)	0.13	1.28 (0.84-1.96)	0.25
Smoking habits				
Non-smoker	1.00			
Ex-smoker	1.02 (0.64-1.64)	0.94		
Current smoker	0.82 (0.45-1.51)	0.53		
Hypertension	2.71 (1.76-4.16)	<0.001	2.13 (1.36-3.33)	0.001
Diabetes	1.68 (1.05-2.69)	0.03	1.21 (0.74-1.98)	0.45
Hypercholesterolemia	4.10 (2.73-6.16)	<0.001	3.85 (2.51-5.88)	<0.001
IPF	2.18 (1.42-3.35)	<0.001	2.64 (1.68-4.14)	<0.001

IPF, idiopathic pulmonary fibrosis; OR, odds ratio; CI, confidence interval.
**Adjusted by age, obesity, hypertension, diabetes, hypercholesterolemia, and IPF (these variables reached the statistical significance of $P < 0.20$ in univariate analysis).*

Table 4. Incidence of newly developed coronary artery disease during follow-up: longitudinal cohort analysis

	No. of subjects*	No. of new events	Unadjusted RR (95% CI)	P	Adjusted RR† (95% CI)	P
Control	1,859	51	1.00		1.00	
IPF	425	17	1.83 (1.04-3.22)	0.04	1.92 (1.08-3.43)	0.03

RR, relative risk; CI, confidence interval; IPF, idiopathic pulmonary fibrosis.
**Case and control subjects with a prior CAD before the index date and insufficient data were excluded from the follow-up analysis, so the number of case and control subjects varies between analyses.*
†Adjusted by age, obesity, hypertension, diabetes, and hypercholesterolemia.

Table 5. Coronary artery disease among the IPF and control group (during the follow-up)

Variable	n (%)
IPF group (n = 17/425)*	
Symptomatic	
Angina pectoris	6 (35)
Acute coronary syndrome	6 (35)
Asymptomatic	5 (29)
Diagnostic method†	
Coronary angiography	10 (59)
Coronary CT angiography	1 (6)
Thallium scan	2 (12)
ECG change and/or abnormal cardiac enzyme	4 (24)
Control group (n = 51/1,859)*	
Angina pectoris	46 (90)
Acute coronary syndrome	5 (10)

IPF, idiopathic pulmonary fibrosis; CT, computed tomography; ECG, electrocardiogram.
**Case and control subjects with a prior CAD before the index date were excluded from the follow-up analysis, so the number of case and control subjects varies between analyses.*
†If there were more than one method used for CAD diagnosis, only the method used for the final diagnosis was described.

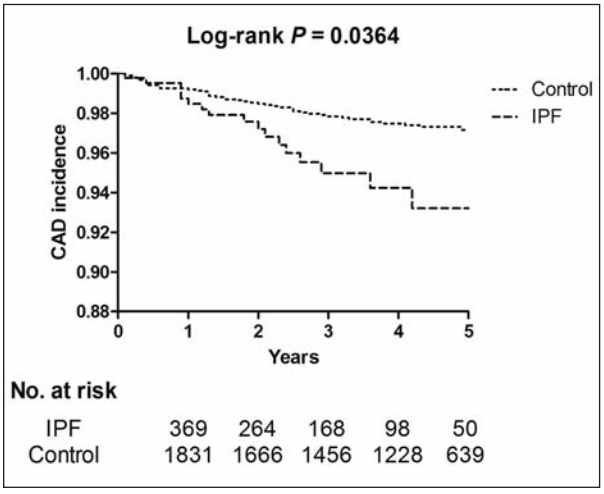

Fig. 1. The cumulative incidence of newly developed coronary artery disease (CAD) in idiopathic pulmonary fibrosis (IPF) and control group during follow up.

CAD except 3 and additional cardiac intervention was done in 48%. About half of the patients with IPF and CAD died and half (54%) of the death was due to lung disease and 12% was due to CAD. Among the newly developed CAD patients, 59% died and one third was cardiovascular death. In control group, 3/51 (6%) of newly developed CAD patients died within 6 months of events occurred. Among 8 patients with asymptomatic CAD (at the time of IPF diagnosis), two patients required intervention; one received percutaneous coronary intervention and survived, but no cardiovascular intervention was done in the other due to acute exacerbation of IPF and died.

Discussion

The present study showed that CAD is more prevalent in the Korean patients with IPF compared to the general population even after the adjustment of multiple cardiovascular risk factors. This strong association between IPF and CAD was also evident during follow-up course. To our knowledge, this is the first large comprehensive study performed in well characterized cohort of IPF and CAD with evaluation of risk factors of CAD and long-term follow-up data. And it is the first report in Asians.

An estimated prevalence of CAD in the United States is about 4-6%, with racial differences (6.1% among whites; 6.0% blacks or African Americans; and 4.3% Asians) (16). According to the data of Korean National Health & Nutrition Examination Survey (17), the prevalence of CAD is 3-4% in Korea. In our study, the prevalence of CAD in general pop-

ulation was 3%. In IPF, it was 7% at the time of IPF diagnosis and this increased risk of CAD continued during follow-up. There were several studies on CAD in IPF in Western countries (10-14). To date, the largest comparative study was a population-based study by Hubbard *et al.*, which evaluated 920 subjects with IPF and 3,593 matched control subjects from the Health Improvement Network in UK (13). They showed increased risk of CAD in IPF compared to the general population before and also after the diagnosis of IPF. However, there was no consideration on the other cardiovascular risk factors such as hypertension, diabetes, and hypercholesterolemia, which might be different in incidence between two groups and affect the development of CAD. And there was some uncertainty about the diagnosis of IPF; they did not mention about the method of diagnosis. Several other studies reported higher risk of CAD in IPF compared to COPD or other fibrotic lung disease (10,11,14). Although known risk factors for CAD were assessed in these studies, the sample size was small and the majority of the patients were far advanced cases (lung transplantation candidates), making it difficult to generalize the study findings to all IPF patients. Furthermore there was no control group in these studies except one which used the patients admitted to general gastroenterology ward as control (12), and no follow-up data were available. Whereas our study enrolled reasonably large number of patients and matched general population and analyzed other known risk factors of CAD with fairly good follow-up data of both groups.

The prevalence of CAD in general population in our study was comparable to the result of our national survey, however, the prevalence of CAD in IPF was lower than that of previous studies in Western countries. Hubbard *et al.* reported a prevalence of 24% (ACS: 8% and angina: 16%) in the subjects with IPF. Among the transplantation candidates, it was 28.6% among 49 cases by Izbicki *et al.*; 65.8% among 73 patients by Nathan *et al.*; 12.4% among 186 patients with fibrotic lung diseases (IPF: 76 cases) by Kizer *et al.*. However, majority of these studies performed coronary angiography as a routine pre-transplantation screening. Actually Nathan *et al.* reported that only 43% of the patients with positive findings at coronary angiography had significant CAD, suggesting that these values might be over-estimated. In other aspect, the estimated prevalence of hypertension is about 60-80%; diabetes 18%; hypercholesterolemia 40-48% in elderly persons of Western countries (18-20), which are relatively higher than the prevalence in our control group (Asian). These differences may partially explain the lower prevalence of CAD in our study.

Diabetes was not an independent risk factor in our study, although hypercholesterolemia was confirmed as a risk factor. Interestingly and also unexpectedly, the prevalence of hypercholesterolemia was significantly lower in IPF than control group. Both the levels of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterols were significantly lower in IPF (Table 1). However, these levels were measured in 360/460 (78%) of IPF group (control group: 96%) and some of the patients were taking statins at the time of sampling. Therefore they may be biased data, but it is interesting and should be confirmed in future studies.

The underlying mechanism of this association between CAD and IPF is unclear. Several studies suggested the endothelial injury by intermittent hypoxia with accelerated atherosclerosis (21), activation of clotting cascade (22), or sharing common cytokines and growth factors between IPF and atherogenesis (23,24) as possible mechanisms. Recently, Kim *et al.* reported that apolipoprotein (Apo) A-I, which is the major apolipoprotein of HDL and known to participate in the anti-inflammatory process (25), was two-fold lower in the bronchoalveolar lavage fluids of IPF group compared with control (26). Moreover, the replacement of Apo A-I prevented the bleomycin induced fibrosis of lung in the animal model. Since the inverse relationship between HDL cholesterol level and the development of CAD is well established (27), Apo A-I and HDL may act as candidate molecules to explain the association between CAD and IPF. In our study, the prevalence of low HDL was significantly higher in the patients with IPF (29% vs. 21%, $P < 0.001$), although the validity of HDL data should be considered.

There are several limitations in our study. First, while the diagnosis of CAD in IPF group was made by thorough review of medical records, it was made only by ICD-10 codes in control group. We could not obtain the data of diagnostic method of CAD in control group, and one may question the validity of diagnosis. However, there was a higher possibility of

over-estimation than under-diagnosis in control group because the diagnosis is related to medical reimbursement. Therefore, any bias resulting from this limitation would tend to underestimate true difference in CAD prevalence between two groups and would not change the conclusion. Second, there is a possibility of more diagnosis of CAD in early preclinical stage due to frequent and thorough medical work-up in IPF than the general population, resulting in overestimation of the association between IPF and CAD. Actually total 13 patients (before or at the time of diagnosis: 8, follow-up: 5) had a diagnosis of CAD in asymptomatic stage. However, the multivariate analysis even after the exclusion of asymptomatic CAD patients showed still significant association between IPF and CAD (OR, 2.02; 95% CI, 1.24-3.29). Furthermore, the patients with IPF may not have symptoms (chest pain on exercise) despite the presence of CAD due to inactivity secondary to dyspnea. Nathan *et al.* reported that unsuspected significant CAD was found by coronary angiography in 18% of IPF patients, which was even higher than in COPD (10.9%, $P < 0.004$). Therefore our 8 patients who had had CAD diagnosis in asymptomatic stage at the time of IPF diagnosis, if not treated, highly likely developed symptom and got CAD diagnosis during follow-up resulting in increasing the incidence of CAD during follow-up. And there was a possibility of asymptomatic CAD also in control group because of frequent routine check-up in general population in Korea. Therefore the possibility of changing the final conclusion by this limitation is not high. Third, the baseline cardiovascular risk factors were different between two groups. The prevalence of these risk factors in the control group was comparable with other reports on Korean general population (28,29). The higher prevalence of diabetes in IPF group was reported before (6), however lower prevalence of hypertension and hypercholesterolemia in IPF group was unexpected and difficult to explain. However, it is unlikely that this might have resulted in false association of IPF and CAD because these known risk factors were less prevalent in IPF group.

In conclusion, our study showed a higher prevalence and incidence of CAD in Korean patients with IPF compared to the general population. And IPF was an independent risk factor of CAD after the adjustment of other possible confounders.

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