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Lung function, coronary artery calcification, and metabolic syndrome in 4905 Korean males

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KEYWORDS
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Computed tomography;
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Summary
Background: Impaired lung function is an independent predictor of cardiovascular mortality. We assessed the relationships of lung function with insulin resistance (IR), metabolic syndrome (MetS), systemic inflammation and coronary artery calcification score (CACS) measured by computed tomography (CT) scan an indicator of coronary atherosclerosis.
Methods: We identified 4905 adult male patients of the Health Promotion Center in Samsung Medical Center between March 2005 and February 2008 and retrospectively reviewed the following data for these patients: pulmonary function, CT-measured CACS, anthropometric measurement, fasting glucose, insulin, lipid profiles, serum C-reactive protein (CRP) and homeostatic model assessment (HOMA-IR). MetS was defined according to the AHA/NHLBI criteria.
Results: When the subjects were divided into four groups according to quartiles of FVC or FEV_1 (% pred), serum CRP level, HOMA-IR, prevalence of MetS and CACS significantly increased as the FVC or FEV_1 (% pred) decreased. The odds ratios (ORs) for MetS in the lowest quartiles

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of FVC and FEV_1 (% pred) were 1.85 (95% CI, 1.49−2.30; $p < 0.001$) and 1.47 (95% CI, 1.20−1.81; $p < 0.001$) respectively. The ORs for the presence of coronary artery calcification in the lowest quartiles of FVC and FEV_1 (% pred) were 1.31 (95% CI, 1.09−1.58; $p = 0.004$) and 1.22 (95% CI, 1.02−1.46; $p = 0.029$) respectively. Obesity, CRP, HOMA-IR, and the presence of coronary artery calcium were independent risk predictors for impaired lung function.
Conclusion: Metabolic syndrome, insulin resistance, coronary atherosclerosis, and systemic inflammation are closely related to the impaired lung function.

Introduction

Impaired lung function, as measured by forced vital capacity (FVC) or forced expiratory volume (FEV_1), is associated with increased incidence and mortality of cardiovascular diseases (CVD).[1−5] Although the mechanisms underlying this association are unknown, it cannot be explained only by the effects of smoking. Several previous studies have suggested that there is a link between impaired lung function and CVD-related factors such as obesity, insulin resistance (IR) or atherosclerosis.[6−9]

Previous approaches exploring the association between lung function and atherosclerosis used carotid intima-media thickness for the noninvasive evaluation of atherosclerosis.[10] Recently, the coronary artery calcium score (CACS) measured by computed tomography (CT) has been frequently used to assess the atherosclerotic plaque burden.[11−13] CACS is a well-accepted, reliable tool for predicting future coronary artery disease.[14]

In addition to associations with individual risk factors, several recent studies have found a positive independent correlation between impaired lung function and metabolic syndrome (MetS).[15−17] However, it is not known whether this relationship holds true in patients with normal lung function.

The objective of this study was to assess the relationship of decreased lung function with a focus on coronary artery calcification, MetS, and other metabolic and inflammatory indices, in Korean males 40 years of age and older without cardiovascular events.

Methods

Study participants

This study was approved by the Institutional Review Board of Samsung Medical Center, and the requirement for patient consent was waived given the retrospective nature of the study.

Data from patients who participated in the annual medical check-up program of the Health Promotion Centre in Samsung Medical Center (a 1250-bed tertiary university hospital in Seoul, South Korea) between March 2005 and February 2008 was used for this study. Inclusion criteria were male gender, age > 40 years, availability of CACS on coronary CT, data to assess the presence of MetS, and data to assess lung function. A total of 5,139 Korean men aged more than 40 years met these criteria. Medical information was gathered through a standardized questionnaire and we excluded subjects with severe cardiovascular disease ($n = 79$), documented acute pharyngitis ($n = 2$), inflammatory bowel disease ($n = 1$), and autoimmune disease ($n = 1$). Current or past smokers were classified as smokers. When the person had more than one visit during this period ($n = 151$, the maximum number of visits the patient had was twice), only the data from the last visit was analyzed. Analysis was performed on a total of 4905 subjects (Fig. 1). During study period, female subjects who met the criteria of our study were only 673, since the CT for CACS is recommended usually for men over 40 years. Considering selection bias, we excluded the data of female subjects.

Measurement of lung function

Spirometry was performed as recommended by the American Thoracic Society[18] using Vmax 22 (SensorMedics, OH, USA). Absolute values of FVC and FEV_1 were obtained and percentage predicted values (% pred) for FEV_1 and FVC were calculated from the following equations obtained in a representative Korean sample.[19]

$$\text{Predicted FVC} = -4.8434 - (0.00008633 \times \text{age}^2(\text{years})) + (0.05292 \times \text{height(cm)}) + (0.01095 \times \text{weight(kg)})$$

$$\text{Predicted } FEV_1 = -3.4132 - (0.0002484 \times \text{age}^2(\text{years})) + (0.04578 \times \text{height(cm)})$$

The highest FVC and FEV_1 value of the three or more tests with acceptable curves was used.

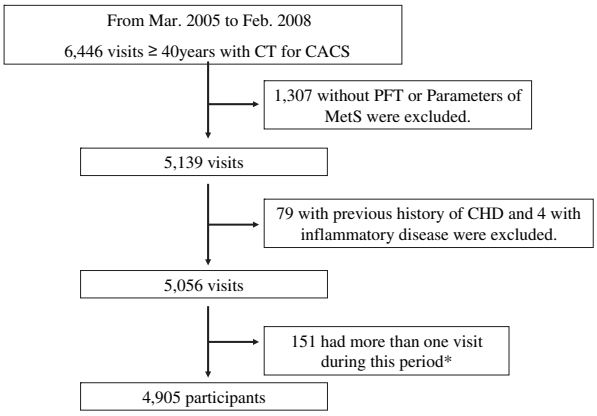

Figure 1 Study flow diagram. CACS, coronary artery calcification score; PFT, pulmonary function test; MetS, Metabolic Syndrome; CVD, cardiovascular disease. *Maximum number of visits the patient had was twice.

Table 1 Clinical characteristics of the study population ($N = 4905$).

Number	
Clinical risk factors	
Age, years	51 (47–57)
Smoking status	
None, %	21.8
Current or past, %	78.2
BMI $\geq$ 25(kg/m^2), %	45.3
Laboratory test	
WBC ($\times 10^3/\mu l$)	5750 (4860–6800)
CRP (mg/dl) ($n = 4779$)	0.07 (0.03–0.13)
FBG (mg/dl)	92 (85–100)
Insulin (μIU/mL)	9.1 (7.1–11.8)
Total cholesterol (mg/dl)	192 (171–214)
LDL-cholesterol (mg/dl)	126 (107–145)
HDL-cholesterol (mg/dl)	51 (44–59)
Triglyceride (mg/dl)	129 (94–185)
Metabolic syndrome, %	23.0
Waist circumference $\geq$ 90 cm, %	38.9
Low HDL cholesterol $<$ 40 mg/dL or specific treatment,%	13.2
Triglycerides $\geq$ 150 mg/dL or specific treatment,%	37.9
SBP $\geq$ 130/DBP $\geq$ 85mmHg or antihypertensive treatment,%	36.8
Fasting glucose $\geq$ 100 mg/dL or diabetes treatment,%	27.3
HOMA-IR ($n = 3861$)	2.1 (1.6–2.9)
Pulmonary function test	
FEV_1/FVC ratio,%	80 (76–84)
FVC % pred	86 (79–93)
FEV_1% pred	88 (80–95)
Coronary artery calcification	
A-CACS mean (interquartile range)	42.8 (0.0–15.3)
Presence of coronary artery calcification, (A-CACS $>$ 0) %	37.2

Values are expressed as percentages, or median (interquartile range). BMI, body mass index; WBC, white blood cell; CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; A-CACS, Agaston coronary artery calcification score.

We analyzed the patients according to the quartiles of FVC or FEV_1 (%pred), and ventilatory patterns defined as restrictive (FEV_1/FVC $\geq$ 70% and FVC $<$ 80%) or obstructive (FEV_1/FVC $<$ 70%) pattern.

Coronary Artery Calcification Score (CACS)

Imaging data for the evaluation of coronary artery calcification was acquired from an ECG-gated 40 channel multidetector CT scanner (Brilliance 40, EBW version 3.02 RRS, Philips Medical Systems, Best, The Netherlands), with a 400 milliseconds gantry rotation time and image reconstruction thickness/interval 2.5 mm/2.5 mm. Agaston coronary artery calcium score (A-CACS) was used for the measurement of CACS.[20] The area of coronary artery calcium was defined as at least four contiguous pixels with a CT density $\geq$130 Hounsfield Units. The total CACS was computed, comprising all calcified lesions in the epicardial coronary system.

Anthropometric measurements and blood tests

Height, weight, waist circumference (WC), systolic (SBP) and diastolic blood pressure (DBP) were measured. Blood pressure was measured according to the Hypertension Detection and Follow-Up Program protocol by using a mercury blood pressure device after the subjects had rested for more than five minutes.[21] For subjects with a SBP higher than 140 mmHg and a DBP higher than 90 mmHg, BP was measured two more times after resting and the average value was used. Height and weight were measured by automatic scale, and body mass index (BMI) was calculated by weight (kg) divided by the squared value of height (m) (kg/m^2). WC was measured at the part of the trunk located midway between the lower costal margin (bottom of lower rib) and the iliac crest (top of pelvic bone) while the patient was standing.

After a 12 h fast, fasting blood glucose (FBG) with the hexokinase method, CRP with turbid immunoassay, total cholesterol (TC), triglyceride (TG) with the enzymatic colorimetric method, high-density lipoprotein cholesterol (HDL-C) with the modified enzymatic method and low-density lipoprotein-cholesterol (LDL-C) with the direct surfactant method were automatically measured using an autoanalyzer (Hitachi, Modular D 2400; Tokyo, Japan). Fasting serum insulin levels were measured by the electrochemiluminescence immunoassay (Hitachi, Roche Modular E 170; Tokyo, Japan), with an intra-assay coefficient of variance of 0.9–1.2% and an inter-assay coefficient of variance of 3.4–4.9%.

IR status was calculated by using the homeostatic model assessment-insulin resistance (HOMA-IR).[22] The calculation formula was as follows:

$$\text{HOMA} - \text{IR} = [\text{fasting insulin } (\mu\text{IU/mL}) \times \text{fasting blood glucose (mmol/L)}]/22.5$$

Diagnosis of Metabolic Syndrome (MetS)

MetS was defined based on the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) with WC defined by the Western Pacific Region of WHO for obesity (WPRO) criteria.[23] The diagnosis of MetS was made when the subjects satisfied more than three of the five categories described below[23]:

1. Abdominal obesity: WC $\geq$ 90 cm;
2. Hypertriglyceridaemia: $\geq$150 mg/dL (1.7 mmol/L);
3. Low HDL-C: $<$40 mg/dL (1.0 mmol/L);
4. Hypertension: $\geq$130/85 mmHg; and
5. Fasting hyperglycaemia: $\geq$100 mg/dL (5.6 mmol/L).

Table 2 Comparisons of HOMA-IR, CRP values, coronary artery calcification score, and prevalence of the metabolic syndrome according to the quartiles of FVC % of predicted value.

	FVC (% pred) quartiles				
	1st (<79%) $n = 1118$	2nd (79–85%) $n = 1254$	3rd (86–92%) $n = 1243$	4th (≥93%) $n = 1290$	p Value for trend
Age, years	55 (50–62)	52 (48–57)	50 (47–55)	49 (46–53)	<0.001
Smoker (%)	80.0	77.6	79.0	76.6	0.108
BMI ≥ 25 kg/m^2, %	55.0	48.4	43.2	35.8	<0.001
Laboratory test					
WBC ($\times 10^3/\mu l$)	6000 (5100–7100)	5765 (4900–6900)	5740 (4900–6700)	5500 (4700–6600)	<0.001
CRP (mg/dl) ($n = 4779$)	0.08 (0.04–0.15) ($n = 1095$)	0.07 (0.04–0.13) ($n = 1228$)	0.06 (0.03–0.12) ($n = 1204$)	0.06 (0.03–0.10) ($n = 1252$)	<0.001
HOMA-IR ($n = 3861$)	2.38 (1.80–3.32) ($n = 832$)	2.21 (1.64–3.04) ($n = 987$)	2.07 (1.58–2.71) ($n = 1008$)	1.97 (1.49–2.49) ($n = 1034$)	<0.001
CAC score					
A-CACS (mean)	72.2	40.8	38.0	24.1	<0.001
Presence of coronary artery calcification (A-CACS >0),%	49.4	38.8	33.7	28.5	<0.001
Components of Metabolic Syndrome					
Waist circumference ≥ 90 cm, %	52.9	41.9	35.5	27.0	<0.001
Low HDL cholesterol < 40 mg/dL or specific treatment, %	14.2	15.3	12.1	11.2	0.004
Triglycerides ≥ 150 mg/dL or specific treatment, %	42.1	41.4	38.2	30.6	<0.001
SBP ≥ 130/DBP ≥ 85 mmHg or antihypertensive treatment, %	46.2	39.5	34.1	28.6	<0.001
Fasting glucose ≥ 100 mg/dL or diabetes treatment, %	34.5	28.9	25.1	21.4	<0.001

Values are expressed as percentages, or median (interquartile range).
FVC, forced vital capacity; BMI, body mass index; WBC, white blood cell; CRP, C-reactive protein; HOMA-IR, homeostatic model assessment-insulin resistance; A-CACS, Agaston coronary artery calcification score; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3 Comparisons of HOMA-IR, CRP values, coronary artery calcification score, and prevalence of the metabolic syndrome according to the quartiles of FEV_1 % of predicted value.

	FEV_1(% pred) quartiles				
	1st (< 80%) $n = 1121$	2nd (80%-87%) $n = 1290$	3rd (88%-94%) $n = 1182$	4th (≥95.0%) $n = 1312$	*p* Value for trend
Age, year	54 (49–60)	51 (47–56)	50 (47–55)	50 (47–55)	<0.001
Smoker, %	83.9	77.9	77.9	73.9	<0.001
BMI ≥ 25 kg/m^2 ,%	45.8	45.7	45.3	44.4	0.483
Laboratory test					
WBC ($\times 10^3/\mu l$)	6050 (5100–7200)	5800 (4900–6900)	5700 (4800–6700)	5540 (4700–6500)	<0.001
CRP (mg/dl) ($n = 4779$)	0.08 (0.04–0.15) ($n = 1094$)	0.07 (0.04–0.13) ($n = 1258$)	0.06 (0.03–0.11) ($n = 1156$)	0.06 (0.03–0.12) ($n = 1271$)	<0.001
HOMA-IR ($n = 3861$)	2.24 (1.65–3.08) ($n = 830$)	2.12 (1.61–2.92) ($n = 1023$)	2.13 (1.64–2.88) ($n = 977$)	2.03(1.55–2.63) ($n = 1031$)	<0.001
CAC score					
A-CACS (mean)	67.7	37.5	36.1	32.9	<0.001
Presence of coronary artery calcification (A-CACS > 0),%	46.9	35.7	33.9	33.3	<0.001
Components of Metabolic Syndrome					
Waist circumference ≥ 90 cm,%	44.7	41.8	37.8	32.0	<0.001
Low HDL cholesterol < 40 mg/dL or specific treatment, %	13.6	14.1	12.6	12.4	0.246
Triglycerides ≥ 150 mg/dL or specific treatment, %	41.0	40.9	37.5	32.8	<0.001
SBP ≥ 130/DBP ≥ 85 mmHg or antihypertensive treatment, %	41.7	38.1	33.4	34.3	<0.001
Fasting glucose ≥ 100 mg/dL or diabetes treatment, %	31.0	27.6	27.2	23.8	<0.001

Values are expressed as percentages, or median (interquartile range).
FVC, forced vital capacity; BMI, body mass index; WBC, white blood cell; CRP, C-reactive protein; HOMA-IR, homeostatic model assessment-insulin resistance; A-CACS, Agaston coronary artery calcification score; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Because obesity is defined as BMI $\geq$ 25 kg/m^2 in Asian populations, BMI in our study was divided with a cut-off point of 25 kg/m^2 for obesity.[24]

Data analysis

To assess whether there was a gradient in various clinical characteristics and laboratory test results across the pulmonary function categories, we used a Mantel—Haenszel test or Jonckheere—Terpstra trend test. Using the highest quartile as the reference group in multivariate logistic regression model, we compared the prevalence of MetS, the individual components of MetS, and the presence of coronary artery calcification across the quartiles of FEV_1 (% pred) and FVC (% pred) after adjustment for confounding factors including age, smoking status and BMI. Among the components of MetS, dyslipidemia was defined as a combination of two components — HDL-C $<$ 40 mg/dL or specific treatment for this lipid abnormality and triglycerides $\geq$ 150 mg/dL or specific treatment for this lipid abnormality. Because the distribution of CRP level was highly skewed, $\log_{10}$-transformed CRP ($\log_{10}$ CRP) values were used for the multivariate analysis.

Values are expressed as percentage of patients or median value (interquartile range). Two-sided *p*-values less than 0.05 were considered statistically significant. SPSS version 11.0 (SPSS Inc, Chicago, IL, USA) and SAS version 9.1 (SAS Institute; Cary, NC, USA) were used for computational analysis.

Results

Clinical characteristics of the study population

The clinical characteristics of the participants are shown in Table 1. Among 4905 study participants in this analysis, the median age (interquartile range) was 51 (47—57) years and 78.2% were current or ex-smokers. The prevalence of MetS was 23.0%. The median (interquartile range) values for the FBG, fasting insulin, and CRP were 92 (85—100) mg/dL, 9.1 (7.1—11.8) μIU/mL, and 0.07 (0.03—0.13) mg/L respectively. Coronary artery calcification was present in 37.2% and the mean A-CACS was 42.8.

Comparisons of HOMA-IR, CRP values, coronary artery calcification score, and the prevalence of the metabolic syndrome according to the quartiles of FVC and FEV_1 % of predicted value

We classified patients according to the quartiles of FVC or FEV_1 (% pred) (Table 2 and 3).

When subjects were grouped by quartiles of FVC or FEV_1 (% pred), median HOMA-IR values significantly increased as the FVC or FEV_1 (% pred) decreased from the fourth quartile to the first quartile. Patients in the lowest FEV_1 or FVC quartiles (Quartile 1) had a significantly higher CRP concentration compared with the other three groups (Quartiles 2, 3, 4). The frequency of coronary artery calcification (A-CACS $>$ 0) as well as the mean values of A-CACS increased as the quartiles of FVC and FEV_1 (% pred) decreased from the fourth quartile to the first quartile ($p < 0.001$, both).

The prevalence of MetS tended also to increase significantly according to the decrement of quartile of FVC (% pred) and FEV_1 (% pred) (Fig. 2A and B) and consistently, the frequency of the individual components of MetS significantly increased as FEV_1 (% pred) and FVC (% pred) quartiles decreased. The one exception was HDL-C in FEV_1 (% pred) quartiles.

Odds ratios for the risk of metabolic syndrome and coronary artery calcification according to quartiles of FVC and FEV_1 % of predicted value adjusted for age, smoking status, and BMI

As shown in Table 4, after adjustment for age, smoking status and BMI, the odds ratio for MetS in the lowest

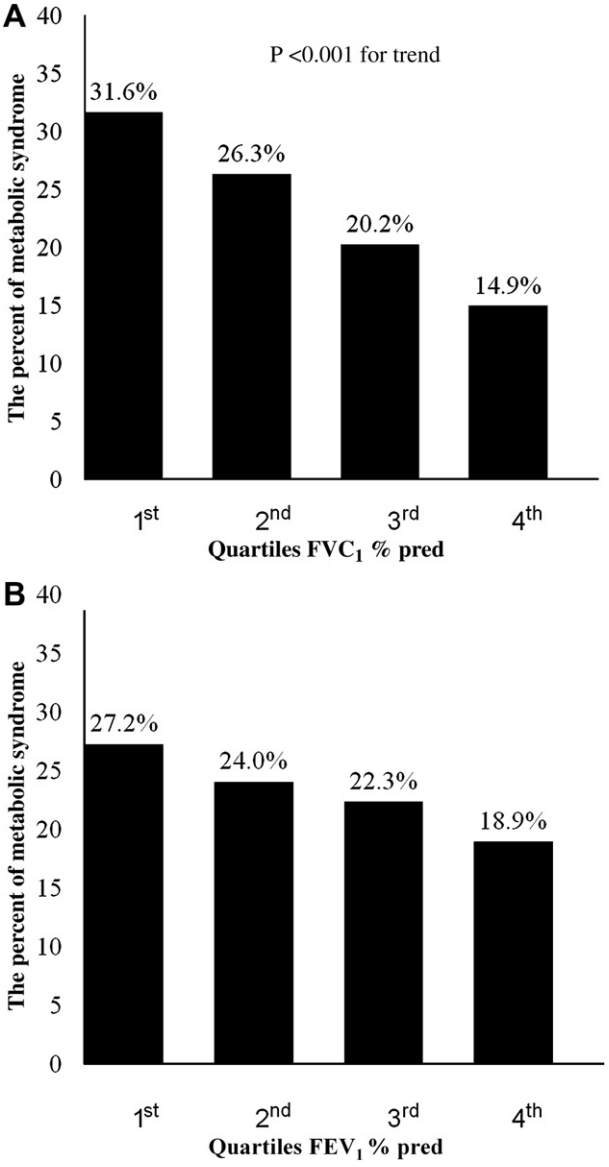

Figure 2 A and B. The prevalence of metabolic syndrome according to decrement of FVC% pred and FEV_1% pred.

quartile of FVC (% pred) and FEV_1 (% pred) was 1.85 (95% CI, 1.49−2.30; $p < 0.001$) and 1.47 (95% CI, 1.20−1.81; $p < 0.001$) respectively, when the highest quartile was considered as 1.

The odds ratio for the presence of coronary artery calcification (A-CACS > 0) in the lowest quartile of FVC (% pred) and FEV_1 (% pred) was 1.31 (95% CI, 1.09−1.58; $p = 0.004$) and 1.22 (95% CI, 1.02−1.46; $p = 0.029$) respectively, when the highest quartile was considered as 1 (Table 4).

Multiple logistic regression analyses with the lowest quartile of lung function or ventilator pattern as the dependent variable

Multiple logistic regression analyses with the adjusted model (age, smoking status, BMI) were developed to determine the relationship between abdominal obesity, CRP, HOMA-IR, and the presence of coronary artery calcification and the presence of the lowest FVC and FEV_1 (% pred) quartile as a dependent variable. Our analyses showed that obesity, higher CRP, higher HOMA-IR, and the presence of coronary artery calcification were independent predictors of the lowest FVC and FEV_1 (% pred) quartiles (Table 5).

In multiple logistic regression analysis with the adjusted model (age, smoking status, BMI) performed for restrictive pattern ($n = 1154$) and obstructive pattern ($n = 306$) as a dependent variable, the central obesity and the presence of coronary artery calcification were an independent factor associated with both restrictive (adjusted OR 1.55, 95% CI 1.26−1.91; $p < 0.001$ and adjusted OR 1.40, 95% CI 1.18−1.66; $p < 0.001$) and obstructive patterns (adjusted OR 1.72 95% CI 1.18−2.50; $p = 0.005$ and adjusted OR 1.37, 95% CI 1.01−1.87; $p = 0.042$). The higher CRP was an independent factor in only obstructive pattern (adjusted OR 1.45, 95% CI 1.01−2.08; $p = 0.042$), while the higher HOMA-IR was significantly associated with only restrictive pattern (adjusted OR 1.19, 95% CI 1.11−1.27; $p < 0.001$).

Discussion

The major findings of this study are that as lung function decreases in Korean men without cardiovascular events over 40 years old, there are significant increases in CACS, MetS, IR and serum CRP. Multiple logistic regression analysis also revealed that the presence of coronary artery calcification, obesity, IR, and CRP are independent risk predictors for the lowest quartile of lung function. These results indicate that lung function, coronary atherosclerosis, MetS, IR, and serum CRP are closely related.

Our study is the first study to use CACS on coronary CT to demonstrate associations between coronary atherosclerosis and reduced lung function in a large population of subjects. Prior studies used carotid atherosclerotic plaque as an indicator of subclinical atherosclerosis.[9,10] Radiographically detectable coronary artery calcification has been known to represent atherosclerotic plaque burden[25] and numerous clinical studies have confirmed that coronary artery calcification is a strong marker of subclinical coronary artery disease.[11−13] In addition, a prospective cohort study of subjects over four ethnic groups reported that CACS is better than carotid intima-media thickness in predicting subsequent cardiovascular disease events.[14]

In this study, we found a significant inverse relationship between lung function and CACS or the presence of coronary artery calcification. Furthermore, the odds ratios for the presence of coronary artery calcification in the lowest quartiles of FVC (% pred) and FEV_1 (% pred) were significantly higher than those in other quartiles even after

Table 4 Odds ratios (95% confidence interval) for the risk of metabolic syndrome and coronary artery calcification according to the quartile of FVC and FEV_1% of predicted value adjusting age, smoking status and BMI.

	FVC (% pred) quartiles				
	1st	2nd	3rd	4th	*p* Value for trend
Metabolic syndrome	1.85 (1.49−2.30)*	1.68 (1.36−2.07)*	1.28 (1.03−1.60)*	1	<0.001
Abdominal obesity (≥90 cm)	2.17 (1.73−2.71)*	1.54 (1.25−1.90)*	1.29 (1.04−1.59)*	1	<0.001
Dyslipidemia	1.67 (1.40−1.99)*	1.50 (1.27−1.77)*	1.30 (1.11−1.53)*	1	<0.001
Impaired glucose metabolism	1.47 (1.22−1.79)*	1.32 (1.09−1.58)*	1.15 (0.95−1.38)	1	<0.001
Elevated blood pressure	1.43 (1.19−1.71)*	1.35 (1.14−1.61)*	1.19 (1.00−1.41)	1	<0.001
Presence of coronary artery calcification (A-CACS >0)	1.31 (1.09−1.58)*	1.23 (1.03−1.46)*	1.14 (0.95−1.36)	1	0.003
FEV_1(% pred) quartiles					
Metabolic syndrome	1.47 (1.20−1.81)*	1.34 (1.10−1.64)*	1.24 (1.005−1.52)*	1	<0.001
Abdominal obesity (≥90 cm)	1.85 (1.49−2.29)*	1.73 (1.41−2.13)*	1.37 (1.11−1.69)*	1	<0.001
Dyslipidemia	1.45 (1.22−1.71)*	1.39 (1.18−1.63)*	1.15 (0.98−1.36)	1	<0.001
Impaired glucose metabolism	1.23 (1.02−1.48)*	1.18 (0.99−1.41)	1.19 (0.99−1.43)	1	0.044
Elevated blood pressure	1.14 (0.96−1.36)	1.16 (0.98−1.36)	0.97 (0.82−1.15)	1	0.044
Presence of coronary artery calcification (A-CACS >0)	1.22 (1.02−1.46)*	1.04 (0.88−1.24)	1.03 (0.87−1.24)	1	0.036

A-CACS, Agaston coronary artery calcification score.
*$p < 0.05$.

Table 5 Multiple logistic regression analysis with lowest quartile of FVC and FEV_1 % of predicted value as dependent variable.

$N = 3736$	Lowest quartile of FVC (% pred)		Lowest quartile of FEV_1 (% pred)	
	Adjusted OR[a](95% CI)	*p* Value	Adjusted OR[a](95% CI)	*p* Value
Abdominal obesity (WC $\geq$90 cm)	1.57 (1.27–1.93)	<0.001	1.29 (1.05–1.59)	0.014
Log_{10} CRP	1.37 (1.11–1.69)	0.003	1.52 (1.24–1.85)	<0.001
HOMA-IR	1.16 (1.09–1.24)	<0.001	1.08 (1.02–1.15)	0.013
Presence of coronary artery calcification (A-CACS > 0)	1.41 (1.19–1.67)	<0.001	1.36 (1.15–1.61)	<0.001

WC, waist circumference; CRP, C-reactive protein; HOMA-IR, homeostatic model assessment-insulin resistance; A-CACS, Agaston coronary artery calcification score; OR, odds ratios; CI, confidence interval.
[a] Adjusted for age, smoking status and body-mass index.

adjustments for confounding factors including age, smoking status, BMI, central obesity, CRP and IR. These findings imply that reduced lung function and coronary atherosclerosis are closely linked.

Another important finding of this study is that, even in patients with predominantly ''normal'' lung function, there was a statistically significant inverse relationship between lung function and various risk factors for CVD including MetS. In earlier reports on lung function and MetS, investigators focused on restrictive lung impairment.[16,17,26] In a recent population-based study, Leone et al.[15] showed a positive independent relationship between lung function impairment (both obstructive and restrictive pattern) and MetS, with abdominal obesity playing a critical role. The findings of Leone et al. is compatible with the result of our study, which central obesity is an independently associated factor with both restrictive and obstructive patterns even after adjustment for other cardiovascular factors, but, the present study goes one step further showing a clear trend of increasing prevalence of MetS with decreasing lung function in Korean men without cardiovascular event. A number of other studies assessed the relationship between CVD-related factors and impaired lung function.[3,6,8,27–29] Sin et al.[3] showed that even a modest decline in FEV_1 (% pred) from a mean of 109–88% was associated with a fivefold increase in CVD mortality. Another study by Lawlor et al.[8] demonstrated that IR assessed by HOMA score decreased by 5% for a one standard deviation increase in log FEV_1 and by 8% for a one standard deviation increase in log FVC. Our data suggests that these trends hold true even in patients who have lung function in the ''normal'' range.

The association between the lung function and cardiac risk factors becomes vividly clear when the lowest quartile and the highest quartile of lung function was compared. Based on our result, the frequency of cardiac risk factors such as central obesity, dyslipidemia, impaired glucose metabolism were significantly higher in the individuals with the lowest quartile of lung function, which helps to estimate that the individuals with the lowest quartile of lung function have more cardiovascular risk than those with the highest quartile of lung function. To predict the 10-year cardiovascular risk, we have calculated Framingham Risk Score (FRS) with factors such as age, smoking, cholesterol, HDL-C, blood pressure and the presence of diabetes in individuals with age < 75 years.[30] The result from the calculated FRS was significantly higher in those with the lowest quartile of lung function than those with the highest quartile of lung function (10% vs. 7% in FVC (% pred); $p < 0.001$ and 10% vs. 8% in FEV_1 (% pred); $p < 0.001$). However, further studies will be necessary to evaluate whether subjects in the lowest quartile of lung function experience a higher incidence of coronary events.

Although the mechanism underlying the relationship between lung function and coronary atherosclerosis, MetS, IR, obesity and CRP remains unclear, there are some plausible explanations. First, the abnormal lung function observed in obese patients may be explained by decreased chest wall compliance and increased peripheral airway resistance.[6] In addition to mechanical factors, adipose tissue is thought be a major source of proinflammatory cytokines and may play an essential role in producing low-grade systemic inflammation.[6,31] It has been reported that the inflammatory biomarker represented by CRP was associated with obstructive or restrictive lung disease as well as obesity.[32,33] Also, the relationship between elevated CRP levels and MetS or IR has been documented.[34,35] Taken together, these reports suggest that systemic inflammation may be an element in the link between lung function impairment and obesity, IR, and MetS. However, it is difficult to draw clear conclusions about a causal relationship based only on the results of this study.

This study has several limitations. It was a retrospective study performed on individuals who voluntarily visited our center for health examinations. Thus, time-dependent relationships between altered WC or coronary artery calcification and pulmonary function could not be observed. Second, because coronary CT was performed in men over 40 years who wanted detailed evaluation for coronary artery disease, our study could reflect some selection bias. However, such selection bias would be low because we excluded men with current or previous histories of angina or myocardial infarction by medical history and the prevalence of metabolic syndrome was similar to prevalence reported in the Korean National Health and Nutrition Examination Surveys (KNHANES).[36] Finally, the present study was conducted at a single center with only male subjects, which might have an influence on the generalization of its findings.

In conclusion, this study clearly showed that coronary atherosclerosis, metabolic syndrome, insulin resistance, and systemic inflammation are closely related to the decreased lung function.

Conflict of interest

This study received no funding or outside support and the authors have no conflict of interest to disclose.

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