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Determinants of respiratory symptom development in patients with chronic airflow obstruction

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KEYWORDS
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Summary
Background: This study was undertaken to identify the determinants of respiratory symptom development in patients with chronic airflow obstruction (CAO).
Methods: Categories of symptomatic and asymptomatic CAO were defined using questionnaire responses and spirometric results. We analyzed data obtained as part of the second South Korean National Health and Nutrition Examination Survey (Korean NHANES II).
Results: Among 187 patients with CAO, 69 had no respiratory symptoms. CAO patients with symptoms were significantly older than those without symptoms ($P = 0.026$), and hypertension was more common among symptomatic CAO patients than among asymptomatic CAO patients ($P = 0.005$). According to questionnaire responses, symptomatic CAO patients had more difficulty in walking or lifting ($P < 0.001$), required more help with personal care ($P = 0.01$), and had poorer

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general health than asymptomatic CAO patients ($P = 0.008$). Symptomatic CAO patients had higher fasting blood glucose levels than asymptomatic CAO patients ($P = 0.028$). Symptomatic CAO patients had significantly lower forced expiratory volume in 1 s (FEV_1) ($P = 0.001$), forced vital capacity (FVC) ($P = 0.008$), and a ratio of FEV_1/FVC than asymptomatic CAO patients ($P < 0.001$). Statistically significant predictors of symptom development were as follows: age (odds ratio (OR) 1.04, $P = 0.028$), hypertension (OR 4.41, $P = 0.008$), fasting blood glucose (OR 1.02, $P = 0.034$), FEV_1 (OR 0.07, $P = 0.002$), FVC (OR 0.08, $P = 0.009$), FEV_1/FVC (OR 0.00, $P = 0.001$). Multiple logistic regression analyses revealed two independent factors associated with symptom development: FEV_1/FVC (OR 0.001, $P = 0.002$) and hypertension (OR 5.95, $P = 0.005$).

Conclusions: In CAO, respiratory symptom development is significantly associated with low FEV_1/FVC and the presence of hypertension.

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Introduction

Chronic obstructive pulmonary disease (COPD) is currently the eighth leading cause of death in Korea.[1] It is the fourth in the United States and is expected to become the third leading cause of death by 2020.[2] Cigarette smoking is the major risk factor. However, despite its importance as a public health problem, COPD is vastly underappreciated. COPD is underdiagnosed and, when diagnosed, commonly undertreated.[3]

Chronic airflow obstruction (CAO) is the main feature of COPD,[4] and undiagnosed airflow obstruction is common in population-based surveys.[5–8] Moreover, the current symptom- or clinically-based definitions of COPD are responsible for underestimations of the prevalence of this disease. Spirometry is being advocated in general practice for the early detection of CAO.[9–11] However, in clinical practice, only patients who present with respiratory symptoms such as a cough, sputum, and/or dyspnea are potential candidates for spirometric testing. The presence of these symptoms encourages patients and physicians to pay attention to airway diseases. Although the early detection of CAO is emphasized, it may be difficult to suspect or diagnose asymptomatic cases of CAO.[12]

Generally, a forced expiratory volume in 1 s (FEV_1) less than 50% of predicted is likely to be associated with impaired general health as well as dyspnea.[3] However, factors other than FEV_1, related to symptom occurrence in CAO patients, have been less well investigated. To identify these symptom determinants, we compared the demographic, socioeconomic, and spirometric data of symptomatic and asymptomatic CAO patients and constructed a logistic regression model. These data used in this study were obtained from the second South Korean National Health and Nutrition Examination Survey (Korean NHANES II).[13]

Methods

Subjects

In Korean NHANES II, a stratified multistage clustered probability design was used to select a representative sample of civilian, non-institutionalized Korean adults aged 18 years and older. We divided Korea into 246,079 areas and, among these, a final 200 survey areas were randomly selected by geographic area, place of residence (urban/rural), and residential pattern (apartment/non-apartment). Finally, this nationwide survey was conducted from selected 12,183 households in 2001. Of 3755 adults of 45 years of age or older, 2101 performed spirometry, and 1673 had more than two acceptable curves. We excluded persons with other respiratory diseases, such as tuberculosis or bronchiectasis by chest radiography, which may affect lung function (Fig. 1).

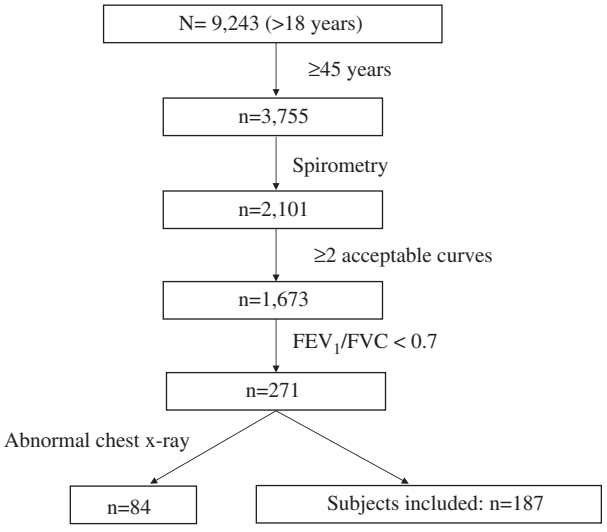

Figure 1 Subject selection process.

Questionnaires and spirometry

The Korean NHANES II consisted of a household questionnaire and a health examination administered by trained examiners. Four categories of questionnaire items were used for this analysis; doctor's diagnosis of COPD or asthma; respiratory symptoms (Table 1); cigarette smoking; and health impact.

Spirometry was performed with equipment that met the American Thoracic Society (ATS) performance criteria.[14] Procedures for testing were based on 1994 ATS recommendations.[14]

Definitions

For this analysis, spirometry results were classified using the Global Initiative for chronic obstructive lung disease (GOLD) criteria.[15] Airflow obstruction was defined by a ratio of an FEV_1 to a forced vital capacity (FVC) (FEV_1/FVC) below 0.7. The severity of ventilatory impairment was classified using GOLD criteria as follows: mild, $FEV_1 \geqslant 80\%$ of predicted; moderate, $50\% \leqslant FEV_1 < 80\%$; severe, $30\% \leqslant FEV_1 < 50\%$; very severe, $FEV_1 < 30\%$. CAO was defined as airflow obstruction in persons aged 45 years or older in the absence of respiratory diseases affecting airflow on chest radiographs.

Using eight questionnaire responses (Table 1), symptomatic patients were defined as persons who presented any one of the following symptoms of cough, sputum, dyspnea, and wheezing, or had a doctor's diagnosis of COPD or asthma. In other words, if any answer was 'yes', the case belonged to symptomatic group.

Statistical analysis

Statistical analysis was performed using SPSS-PC for Windows Version 11.0. Descriptive data are expressed as mean (SD) and frequencies are expressed as number (%). Differences between the two groups were tested using the Student *t*-test or the χ^2-test. Determinants of respiratory symptom development in patients with CAO were identified using multiple logistic regression analyses. *P*-values of <0.05 were used to define statistical significance.

Results

Of 271 subjects with an FEV_1/FVC of less than 0.7 by spirometry, 84 were excluded because of the presence of lung lesions by chest radiography. Finally, 187 were included using our definition of CAO (Fig. 1), and of these 69 were asymptomatic.

Symptomatic CAO patients were significantly older than asymptomatic patients ($P = 0.026$), and hypertension was more common among symptomatic than among asymptomatic patients ($P = 0.005$) (Table 2).

In terms of life-style factors, e.g., smoking habit and economic status, no difference was observed between the two patient groups (Table 3).

Symptomatic CAO patients had more difficulty in walking or lifting ($P<0.001$), needed more help with personal care ($P = 0.01$), and had poorer general health than asymptomatic patients ($P = 0.008$) (Table 4).

Laboratory tests showed that symptomatic CAO patients had higher fasting blood glucose levels than asymptomatic patients ($P = 0.028$) (Table 5).

Spirometry tests showed that symptomatic CAO patients had significantly lower FEV_1 ($P = 0.001$), FVC ($P = 0.008$), FEV_1/FVC than asymptomatic CAO patients ($P<0.001$). No asymptomatic patient had severe airflow obstruction, defined as an FEV_1 of $<50\%$ of predicted (Table 6).

Table 1 Questionnaires for respiratory symptoms and physician-diagnosed respiratory diseases.

Items
1. Has a doctor ever told you that you had chronic bronchitis, emphysema, or COPD?
2. Do you bring up phlegm on most days for 3 consecutive months or more during the year?
3. Do you usually cough on most days for 3 consecutive months or more during the year?
4. Are you troubled by shortness of breath when hurrying on level ground or walking uphill?
5. Has a doctor ever told you that you had asthma?
6. Have you had wheezing or whistling in your chest at any time during the last 12 months?
7. Have you had an attack of asthma (sudden bouts of cough and shortness of breath with wheezing) in the last 12 months?
8. Are you currently taking any medication, (including inhalers, aerosols or tablets) for asthma, chronic bronchitis, emphysema or COPD?

COPD, chronic obstructive pulmonary disease.

Table 2 Demographic characteristics in CAO* patients with or without symptom.

Variable	No symptom ($n = 69$)	Symptom ($n = 118$)	*P*-value
Age (years)	61.0±9.7	64.0±8.5	0.026
Male sex, *n* (%)	52 (75.4)	94 (79.7)	NS
Height (cm)	163±8	163±8	NS
Weight (kg)	61.6±10.7	61.6±9.1	NS
Body mass index (kg/m^2)	23.0±2.9	23.1±2.8	NS
Waist to hip ratio	0.90±0.07	0.92±0.06	NS
Systolic blood pressure (mmHg)	130±18	131±21	NS
Diastolic blood pressure (mmHg)	82±11	79±11	NS
Associated disease†			
Hypertension, *n* (%)	4 (5.8)	25 (21.4)	0.005
Diabetes mellitus, *n* (%)	1 (1.4)	9 (7.7)	NS
Arthritis, *n* (%)	11 (15.9)	25 (21.2)	NS

Values are expressed as mean±SD unless otherwise specified.
CAO, chronic airflow obstruction; NS, not significant.
*Age⩾45, $FEV_1/FVC < 0.7$, and no other lesion causing airflow obstruction in chest radiograph.
†Subjects who have already taken some medication for an associated disease.

Table 3 Lifestyle and economic status in CAO patients with or without symptom.

Variable	No symptom ($n = 69$)	Symptom ($n = 118$)	*P*-value
Smoking			NS
Smoker, *n* (%)	50 (72.5)	83 (70.3)	
Current smoker, *n* (%)	34 (49.3)	56 (47.4)	
Ex-smoker, *n* (%)	16 (23.2)	27 (22.9)	
Never, *n* (%)	19 (27.5)	35 (29.7)	
Age to start smoking (years)*	22.4±6.3	22.0±5.0	NS
Smoking duration (years)*	35.5±11.8	38.4±11.5	NS
Pack-years*	23.2±23.7	24.9± 22.2	NS
Smoking cessation attempt*, *n* (%)	11 (15.9)	27 (22.9)	NS
Passive smoking, *n* (%)	27 (39.1)	50 (42.4)	NS
Regular exercise, *n* (%)	22 (31.9)	29 (24.6)	NS
Walking time (min/day)	112±207	71±86	NS
Working time (days/week)†	5.9±1.3	5.9±1.4	NS
Working time (h/day)†	8.6±2.8	8.8±2.8	NS
Sleep (h/day)	6.8±1.7	6.8±1.5	NS
Health examination, *n* (%)	36 (52.2)	59 (50.0)	NS
Living expenses (US$/month)	760±568	705±507	NS
Income (US$/month)	975±890	891±722	NS

Values are expressed as mean±SD unless otherwise specified.
NS, not significant.
*Excluding those subjects who never smoked.
†Including those subjects with job (no symptom, $n = 6$; symptom, $n = 33$).

The statistically significant predictors of symptom development by bivariate analyses were as follows: age (odds ratio (OR) 1.04, $P = 0.028$), hypertension (OR 4.41, $P = 0.008$), fasting blood glucose (OR 1.02, $P = 0.034$), FEV_1 (OR 0.07, $P = 0.002$), FVC (OR 0.08, $P = 0.009$), and FEV_1/FVC (OR 0.00, $P = 0.001$) (Table 7). However, multiple logistic regression analyses revealed that two independent factors were associated with symptom development, i.e., FEV_1/FVC (OR 0.001; 95% confidence interval (CI) 0.00–0.07, $P = 0.002$) and hypertension (OR 5.95; 95% CI 1.69–20.95, $P = 0.005$).

Table 4 Health impact in CAO patients with or without symptom.

Variable	No symptom ($n = 69$)	Symptom ($n = 118$)	*P*-value
Weight loss	13 (18.8)	32 (27.1)	NS
Difficulty in walking or lifting			<0.001
No	40 (58.8)	36 (30.5)	
Some	24 (35.3)	51 (43.2)	
Much	2 (2.9)	29 (24.6)	
Unable	2 (2.9)	2 (1.7)	
Help handling personal care			0.01
No need	67 (100)	106 (90.6)	
Need	0 (0)	11 (9.4)	
General health			0.008
Excellent	4 (5.8)	5 (4.2)	
Very good	30 (43.5)	26 (22.0)	
Good	18 (26.1)	36 (29.7)	
Fair	16 (23.2)	39 (33.1)	
Poor	1 (1.4)	13 (11.0)	

Values are expressed as number (%).

Table 5 Biochemical characteristics in CAO patients with or without symptom.

Variable	No symptom ($n = 69$)	Symptom ($n = 118$)	*P*-value
Hemoglobin (g/dL)	13.9±1.3	14.9±8.0	NS
Hematocrit (%)	42.3±4.1	43.3±6.7	NS
AST (IU/L)	25.8±10.1	24.8±9.2	NS
ALT (IU/L)	20.4±9.6	21.4±12.2	NS
Total cholesterol (mg/dL)	203±34	194±31	NS
Triglyceride (mg/dL)	159±85	154±79	NS
HDL cholesterol (mg/dL)	47.6±13.1	44.1±11.1	NS
Fasting blood glucose (mg/dL)	94±15	100±20	0.028
Hemoglobin A1c (%)	5.7±0.5	7.6±12.1	NS
Blood urea nitrogen (mg/dL)	13.8±3.8	14.6±4.0	NS
Creatinine (mg/dL)	1.1±1.1	1.1±0.8	NS

Values are expressed as mean±SD.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; NS, not significant.

Table 6 Lung function parameters and severity of airflow obstruction in CAO patients with or without symptom.

Variable	No symptom ($n = 69$)	Symptom ($n = 118$)	*P*-value
FEV_1 (% predicted)	84.9±15.2	75.3±21.6	0.001
FVC (% predicted)	99.2±14.0	92.3±18.3	0.008
FEV_1/FVC (%)	64.6±5.8	59.6±10.1	<0.001
COPD severity*			0.004
Mild, *n* (%)	44 (63.8)	55 (46.6)	
Moderate, *n* (%)	25 (36.2)	44 (37.3)	
Severe, *n* (%)	0 (0)	16 (13.6)	
Very severe, *n* (%)	0 (0)	3 (2.5)	

Values are expressed as mean±SD unless otherwise specified.
FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.
*GOLD[15] criteria as follows: mild, $FEV_1 \geqslant 80\%$ of predicted; moderate, $50\% \leqslant FEV_1 < 80\%$; severe, $30\% \leqslant FEV_1 < 50\%$; very severe, <30%

Table 7 The association between variables and the occurrence of symptoms in patients with airflow obstruction.

Variable	Odds ratio (95% confidence interval)	*P*-value
Age (years)	1.04 (1.004–1.07)	0.028
Hypertension	4.41 (1.47–13.28)	0.008
Fasting blood glucose (mg/dL)	1.02 (1.002–1.04)	0.034
FEV_1% predicted	0.07 (0.01–0.39)	0.002
FVC % predicted	0.08 (0.01–0.54)	0.009
FEV_1/FVC (%)	0.00 (0.00–0.04)	0.001

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Discussion

Sixty-nine patients who had neither symptom nor doctor's diagnosis of COPD or asthma had significant airflow limitation by spirometry testing even though all of them showed mild to moderate airflow obstruction according to the GOLD criteria.[15]

Bivariate analyses showed that age, hypertension, fasting blood glucose, FEV_1, FVC, and FEV_1/FVC were significantly associated with symptom occurrence in CAO. Although old age, hypertension, and high fasting blood glucose levels are not directly related to respiratory symptoms and/or airway obstruction, all might encourage an individual to seek a doctor's advice,[16,17] and if spirometry is performed, airflow obstruction would probably be diagnosed.

It can be presumed that the degree of ventilatory impairment affects subjective symptoms. In the present study, no severe airflow obstruction (defined as an FEV_1 of $<50\%$ of predicted) was observed in asymptomatic subjects. Bivariate analyses showed that each of the three spirometric parameters was negatively associated with symptom occurrence in CAO patients. However, multiple logistic regression analyses revealed that FEV_1/FVC was the most significant factor of these factors. FEV_1/FVC is known to be able to reflect obstructive ventilatory impairment better than FEV_1.[18] Because FEV_1/FVC is a ratio, mild to moderate obstructive disease can be identified without having to refer to predicted values. Although severe CAO patients have usually a low FVC and a low FEV_1, FVC is not considered as a marker of airflow obstruction.

In the present study, hypertension was the second independent factor associated with symptom occurrence in CAO. Tobacco smoking is an etiologic factor of both COPD and systemic hypertension, and is known to increase the impact of hypertension as a risk factor for cardiovascular disease.[19] Epidemiologic studies have shown airflow limitation to be an independent predictor of future cardiovascular events in patients with various cardiovascular risk factors.[20,21] Moreover, isolated systolic hypertension and emphysema may frequently co-occur in the elderly, as both conditions are strongly related to an advancing age.[22]

Of 168 subjects with mild to moderate airflow obstruction defined as $FEV_1 \geqslant 50\%$ of predicted, 41% were completely asymptomatic. Vestbo and Lange[23] followed patients with GOLD stage 0 and found that 11.6% and 18.5% of patients without respiratory symptoms developed GOLD stage 1 or worse after 1 and 15 years, respectively. Moreover, Renwick and Connolly[24] demonstrated that respiratory symptoms do not predict airflow obstruction, and concluded that respiratory symptoms do not identify adults with airflow obstruction. These findings are consistent with our data that 37% of CAO patients were asymptomatic and had never been spirometry tested. These results suggest that spirometric testing is mandatory for detection of early stage of CAO. Previous studies conducted in general practice have demonstrated that spirometry significantly improves COPD early detection rates in general practice.[11,12]

The occurrence of respiratory symptoms can make a patient aware of CAO and probably predicts more severe airway disease. However, the absence of symptoms is no indicator of the absence of CAO. Of note, almost 10% of our subjects with CAO were not only asymptomatic but were also never-smokers (Table 3). Even in a national sample of adults in the United States, undiagnosed airflow obstruction was more common than doctor-diagnosed COPD or asthma, and 12.2–35.2% of women with airflow obstruction had never smoked.[3] Moreover, among 1315 subjects without airflow obstruction who responded eight respiratory questionnaires, 771 (58.6%) were symptomatic. This means that symptom does not predict airflow obstruction. Although a consensus statement from the National Lung Health Education Program recommended that primary-care providers should

perform office spirometry tests for smokers of $\geqslant$45 years in order to detect COPD,[10] spirometry testing should be applied to diagnose COPD at the earliest possible opportunity in all subjects of $\geqslant$45 years of age, irrespective of cigarette smoking.

In conclusion, FEV_1/FVC was identified as the most important determinant of symptom occurrence in CAO, and hypertension as the second most important. Perhaps this means that hypertensive subjects are more likely to be diagnosed as having CAO than normotensive subjects. More than a third of our subjects with CAO were asymptomatic and without a doctor's diagnosis of COPD or asthma, even though they had an FEV_1 of $\geqslant$50% of predicted. We conclude that currently, spirometry is the only diagnostic tool capable of detecting early CAO in asymptomatic subjects.

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