Factors Influencing Cognitive Function in Subjects With COPD

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BACKGROUND: The aim of this study was to assess the association between cognitive function and age, pulmonary function, comorbidity index, and the 6-min walk distance in subjects with COPD as well as to compare the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) in terms of their ability to identify cognitive dysfunction in subjects with COPD. METHODS: A total of 52 individuals with stable COPD were included in this study. Cognitive function was assessed using MMSE and MoCA. Age, body mass index, the Modified Cumulative Illness Rating Scale, 6-min walk distance, arterial blood gases, and pulmonary function tests were assessed and recorded. RESULTS: The range and SD of scores in subjects with COPD were larger with MoCA than with MMSE. MMSE and MoCA scores are associated with 6-min walk distance and comorbidity index in subjects with COPD. General cognitive function measured by MoCA was negatively correlated with the comorbidity index but was positively associated with 6-min walk distance in subjects with COPD after controlling for possible confounding factors in the multivariate model. However, general cognitive function measured by MMSE was not correlated with the comorbidity index and 6-min walk distance in subjects with COPD, after controlling for possible confounding factors in the multivariate model. CONCLUSIONS: MoCA may be a more reliable screening test than MMSE in detecting cognitive impairment in subjects with COPD. The addition of cognitive tests on assessment of subjects with COPD can provide further benefit. *Key words: cognitive function; chronic obstructive pulmonary disease; mini-mental state examination; Montreal cognitive assessment.* [Respir Care 2016;61(8):1044–1050. © 2016 Daedalus Enterprises]

Introduction

COPD is a slowly progressive lung disease with a vast array of extrapulmonary effects, including those on cognitive function.[1,2] The consequences of cognitive impairment occurring more frequently in elderly patients are not well known.[3,4] Cognitive impairment, which is a common occurrence in individuals with COPD, may be associated with increased mortality and morbidity.[5] In these patients, hypoxia associated with COPD may be a contributing factor in the development of cognitive impairment through reduced cerebral perfusion.[6] Previous studies suggested that >50% of the subjects with mild cognitive impairment may exhibit progression to dementia within a 3–5-y period.[7,8] Thus, since mild cognitive impairment may indicate an increased risk of impending dementia, its identification could lead to implementation of secondary prevention strategies by controlling risk factors.[7,9] In this regard, early detection of cognitive impairment in patients with COPD also bears clinical importance.

This study was undertaken to assess the association between cognitive function and age, pulmonary function, comorbidity index, and the 6-min walk distance in subjects with COPD as well as to compare the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) in terms of their ability to identify cognitive dysfunction in subjects with COPD.

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The authors have disclosed no conflicts of interest.

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Methods

Patients regularly followed up in the respiratory disease out-patient unit of our institution between January 2013 and July 2013 were included in this study. The study protocol was approved by the local ethics committee, and written informed consent was obtained from all subjects enrolled in the study. Groups A, B, C, and D were defined on the basis of the classification scheme proposed by the Global Initiative for Chronic Obstructive Lung Disease in 2013.[10] Exclusion criteria for patients with COPD included: (1) exacerbation of respiratory symptoms in the past 4 weeks (change in dyspnea and/or volume/color of sputum, need for antibiotic treatment, or need for hospitalization); (2) presence of asthma, unstable coronary heart disease, uncontrolled diabetes, hypertension, left-sided congestive heart failure, neoplasia, severe claudication, encephalitis, or epilepsy; (3) history of head injury or brain tumor; (4) presence of a major psychiatric condition according to the American Psychiatric Association[11]; and (5) presence of dementia as defined by American Psychiatric Association criteria.[11]

Education

The education level of all subjects was ascertained. Education level was classified as follows: no education = 1; primary school = 2; high school = 3; university = 4.

Pulmonary Function Tests

Following a general clinical examination, pulmonary function of the study subjects were evaluated. After recording sex, height, and weight, an investigator from the study team performed spirometry on each subject with a portable dry rolling SpiroBank spirometer (Medical International Research, Rome, Italy) in accordance with the recommendations of the American Thoracic Society and calculated the results on the basis of predicted values.[12,13] Percent predicted FVC, FEV_1, and FEV_1/FVC were recorded.

Blood Gas Analyses

Before measurements, the blood gas monitoring device utilized for study purposes (EasyStat, Medica Coporation, Bedford, MA) was calibrated according to the manufacturer's instructions. Radial arterial blood (while breathing room air) was aspirated with a heparinized syringe, placed on ice, and taken to a blood gas laboratory for analyses, which were completed within 10 min of sampling.

QUICK LOOK

Current knowledge

Cognitive impairment is a frequent occurrence in patients with COPD. Previous studies have reported discrepant results on the relation between arterial blood gases, pulmonary function tests, and cognitive function.

What this paper contributes to our knowledge

Subjects with COPD with better functional capacity and lower comorbidity had better cognitive function. The Montreal Cognitive Assessment may be a more reliable screening test than the Mini Mental State Examination in identifying cognitive impairment in subjects with COPD.

6-Min Walk Test

At the beginning of the test, the subjects' vital signs, including heart rate, blood pressure, and breathing frequency, were measured. The S_{pO_2} was also noted. The 6-min walk test was performed according to the American Thoracic Society guidelines.[14] Subjects were asked to walk at their own pace, along a 30-m-long straight hospital corridor. Subjects were asked to walk as much distance as possible in 6 min and were allowed to stop if they developed severe dyspnea, chest pain, dizziness, diaphoresis, or leg cramps during the test. However, subjects were asked to resume walking as soon as possible, if they could. At the end of 6 min, subjects were asked to stop, and vital signs (blood pressure, heart rate, and breathing frequency) were assessed again. S_{pO_2} was also assessed immediately after the participants stopped walking. No feedback was given during the test.

Mini Mental State Examination

The MMSE, a rater-administered screening tool, evaluates the general cognitive status of an individual. The 20 items produce scores ranging between 0 and 30 (scores of >24 are considered normal). Published reference values are 27.6 ± 1.7 for healthy subjects[15,16] and 27.0 ± 1.8 for subjects with COPD.[11] The MMSE was used to provide an overall measure of cognitive function because it is closely linked to more extensive memory testing and cognitive decline in the COPD population.[17,18]

Montreal Cognitive Assessment

The MoCA was designed as a rapid screening instrument for mild cognitive dysfunction.[19] It assesses different

cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time required to administer MoCA is approximately 10 min. The maximum total score is 30 points; a score of ≥21 is considered normal according to the validated Turkish version.[20]

The Modified Cumulative Illness Rating Scale

The Modified Cumulative Illness Rating Scale is a comprehensive recording of all comorbid diseases of a patient. It classifies comorbidities by 14 organ systems affected and rates them from 0 to 4 according to their severity. Within each category, when 2 diseases are present, the disease with the higher score is counted. We generated 4 ratings for each subject, according to the instructions of the Modified Cumulative Illness Rating Scale: total score, number of categories endorsed, severity index (total score/number of categories endorsed), and number of categories at level 3.[21]

Statistical Analyses

All clinical parameters were expressed as mean ± SD. Student *t* and Mann-Whitney tests were performed to assess group differences in continuous data. Education level was classified as follows: no education = 1; primary education = 2; high school graduate = 3; university graduate = 4. Categorical variables were compared using chi-square tests. Bivariate analyses were performed with Pearson correlations. Multiple stepwise linear regressions were performed to determine the relative contributions of potential confounding factors in cognitive function tests. $P < .05$ was considered to be statistically significant.

Results

There were a total of 52 participants in the study, ranging in age from 43 to 79 y. Of the subjects with COPD, 47 were male and 5 were female. The range and SD of scores was larger with MoCA (11–27, 3.6) than with MMSE (17–30, 2.5). Also a more pronounced ceiling effect was found for MMSE (one subject had a score of 30) as compared with MoCA (0 subjects had a score of 30).

The proportion of subjects with cognitive impairment as determined by MoCA was 30.8% (16 of 52), whereas the corresponding figure was 25% (13 of 52) for MMSE. Thus, more subjects were categorized as having cognitive impairment with MoCA than with MMSE.

Cognitive impairment as assessed by MoCA was present in 12.5% ($n = 1$ of 8), 32.4% ($n = 12$ of 37, $P = .27$), and 42.9% ($n = 3$ of 7, $P = .23$) of Group A, B, and D, respectively, subjects with COPD, as determined on the basis of the Global Initiative for Chronic Obstructive Lung Disease 2013 staging system. Despite a slight increase in the proportion of individuals with cognitive impairment from Group A COPD to Group D COPD, this difference did not reach statistical significance according to the chi-square test. The corresponding figures for the proportion of subjects with cognitive impairment as measured by MMSE in Group A, B, and D subjects with COPD were 12.5% ($n = 1$ of 8), 29.7% ($n = 11$ of 37, $P = .32$), and 14.3% ($n = 1$ of 7, $P = .92$), respectively.

Table 1. Characteristics of COPD Subjects With Cognitive Impairment Measured by Montreal Cognitive Assessment

Characteristics	Subjects With Cognitive Impairment ($n = 16$)	Subjects Without Cognitive Impairment ($n = 36$)	*P*
Age, y	64.9 ± 9.4	59.4 ± 8.7	.046
BMI, kg/m^2	28.2 ± 4.0	25.9 ± 5.0	.10
Education level*	1.7 ± 0.6	2.3 ± 0.7	.01
FEV_1, % predicted	50.5 ± 17.2	55.7 ± 23.3	.42
P_{aO_2}, mm Hg	69.1 ± 13.2	71.5 ± 11.0	.51
P_{aCO_2}, mm Hg	37.7 ± 6.8	36.6 ± 5.0	.52
6-min walk distance, m	393.5 ± 79.5	444.1 ± 124.2	.14
MCIRS	23.1 ± 3.7	20.3 ± 2.7	.004

Data are mean ± SD.
* Education level was classified as follows: no education = 1; primary school = 2; high school = 3; university = 4.
BMI = body mass index
MCIRS = Modified Cumulative Illness Rating Scale

Also, the proportion of subjects with COPD with cognitive impairment in disease severity groups defined on the basis of FEV_1[22] were examined. In this regard, cognitive impairment as determined by MoCA was found to be present in 16.7% ($n = 1$ of 6), 31.8% ($n = 7$ of 22, $P = .48$), 37.5% ($n = 6$ of 16, $P = .33$), and 25% ($n = 2$ of 8, $P = .73$) of individuals with mild, moderate, severe, and very severe COPD according to the FEV_1 results. The difference in the proportion of subjects with cognitive impairment between these severity groups was not statistically significant, as suggested by the chi-square test. The corresponding figures according to MMSE in mild, moderate, severe, and severe COPD groups defined on the basis of FEV_1 results were 16.7% ($n = 1$ of 6), 31.8% ($n = 7$ of 22, $P = .48$), 31.3% ($n = 5$ of 16, $P = .51$), and 0% ($n = 0$ of 8, $P = .36$), respectively, again with no statistically significant differences between the groups.

Subjects with COPD with cognitive impairment measured by MoCA had a lower 6-min walk distance and higher comorbidity index than subjects with COPD without cognitive impairment (Table 1). Similarly, subjects with COPD with cognitive impairment measured by

Table 2. Characteristics of COPD Subjects With Cognitive Impairment Measured by Mini Mental State Examination

Characteristics	Subjects With Cognitive Impairment ($n = 13$)	Subjects Without Cognitive Impairment ($n = 39$)	P
Age, y	69.0 ± 5.8	58.5 ± 8.6	.001
BMI, kg/m^2	28.4 ± 4.1	26.0 ± 4.9	.11
Education level*	1.7 ± 0.7	2.2 ± 0.7	.04
FEV_1, % predicted	55.0 ± 17.4	53.8 ± 23.0	.84
P_{aO_2}, mm Hg	68.6 ± 10.8	71.5 ± 11.9	.44
P_{aCO_2}, mm Hg	36.8 ± 4.1	37.1 ± 6.1	.86
6-min walk distance, m	389.4 ± 97.5	441.5 ± 117.2	.15
MCIRS	23.1 ± 4.2	20.5 ± 2.7	.01

Data are mean ± SD.
* Education level was classified as follows: no education = 1; primary school = 2; high school = 3; university = 4.
BMI = body mass index
MCIRS = Modified Cumulative Illness Rating Scale

MMSE had a higher comorbidity index and higher age than subjects with COPD without cognitive impairment (Table 2).

There was a negative relationship between age, comorbidity index, and cognitive performance, whereas a positive relationship between 6-min walk distance and cognitive performance was observed (Table 3). None of the severity measures for COPD (pulmonary function tests and arterial blood gases) were associated with the risk of cognitive impairment.

General cognitive function, as measured by MoCA, correlated negatively with the comorbidity index, whereas it was positively correlated with the 6-min walk distance in subjects with COPD, after controlling for possible confounding factors in the multivariate model (Table 4). There were no significant associations between comorbidity index, 6-min walk distance, and cognitive function as assessed by MMSE in the multivariate model (Table 5). MoCA according to Tables 4 and 5 is associated with more clinical parameters than MMSE.

Discussion

In this study, we demonstrated that MoCA, as compared with MMSE, is less prone to ceiling effects in subjects with COPD and classifies more subjects as having cognitive impairment. Furthermore, the range and SD of scores were larger with MoCA than with MMSE, and MoCA is associated with more clinical parameters than MMSE. Thus, it appears that MoCA may be considered to represent a more reliable screening test than the MMSE in detecting cognitive impairment in subjects with COPD.

The proportion of subjects with COPD with cognitive impairment as measured by MoCA was 12% in the current study, with an increase in the rate of cognitive impairment from mild to very severe COPD, although the difference between the severity groups was statistically insignificant. The prevalence of cognitive dysfunction in subjects with COPD was examined in 2 previous studies. A study involving 45 subjects with moderate to severe COPD and 50 healthy controls found that mild cognitive impairment was present in 36% (16 of 45) of subjects with COPD, in comparison with 12% (6 of 50) of control subjects.[23] In a study evaluating the prognostic role of cognitive impairment in subjects with severe COPD, the prevalence of overall cognitive impairment, as defined by MMSE, was 10.4%.[4] Clearly, a significant discrepancy is present within this limited number of studies.

General cognitive function, as measured by MoCA, correlated negatively with the comorbidity index, whereas it correlated positively with the 6-min walk distance in subjects with COPD in the multivariate model. Accordingly, a reduction in the functional level and increased comorbidity seemed to be predictive of a decline in cognitive functioning. However, no significant associations were found between these factors and cognitive function as assessed by MMSE. Consistent with these observations, a study in 45 subjects with moderate to severe COPD found superiority of MoCA over MMSE in detecting mild cognitive impairment.[23] Use of different cognitive tests was associated with a difference in study results. Previous studies on the relationship between cognitive function and COPD generally yielded conflicting results. In a study in an older COPD population, the 6-min walk test and pulmonary function tests were predictive of cognitive performance on various tasks.[24] According to the authors, older individuals who have COPD may be affected in 3 ways that are relevant to cognitive functioning. They may experience age-related declines in blood flow, disease-related declines in arterial oxygen content, and both age- and disease-related declines in physical activity.[24] Our results are partly in agreement with these findings. On the other hand, another study investigating the relationship between aerobic fitness and cognition in a sample of subjects with COPD found that no significant relationships between exercise levels attained and any of the cognitive variables.[25] In a study evaluating cognitive function 1 y after hospitalization in subjects ≥65 y old without cognitive impairment at baseline, cognitive decline (an MMSE score) was associated with higher comorbidity (Charlson comorbidity index) and reduced functional level.[26] In contrast, in a study examining the predictors of cognitive decline in subjects with hypoxemic COPD on continuous oxygen therapy over the course of a 2-y period, loss

Table 3. Simple Correlation Between Cognitive Function and Clinical Factors

	Age		6MWD		MCIRS		% Predicted FEV_1		BMI		P_{aO_2}		P_{aCO_2}		Education	
	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*
MoCA	−0.41	.002	0.39	.004	−0.50	<.001	0.17	.21	−0.16	.24	.18	.20	−0.11	.42	0.60	<.001
MMSE	−0.38	.005	0.29	.037	−0.40	.003	0.05	.71	−0.24	.007	.07	.60	−0.12	.36	0.51	<.001

6MWD = 6-min walk distance
MCIRS = Modified Cumulative Illness Rating Scale
BMI = body mass index
MoCA = Montreal Cognitive Assessment
MMSE = Mini Mental State Examination

Table 4. Multivariate Model With Cognitive Function, Measured by Montreal Cognitive Assessment as Dependent Variable and 6-Min Walk Distance, Comorbidity Index, Pulmonary Function, and P_{aO_2} as Independent Variables

Characteristics	Cognitive Function Values	
	β*	*P*
Intercept	$R^2 = 0.62$	<.001
Age	−0.10	.34
Gender (male)	0.31	.002
Education level	0.43	<.001
BMI	−0.01	.86
6-min walk distance	0.20	.033
MCIRS	−0.25	.011
FEV_1, % predicted	−0.12	.23
P_{aO_2}	−0.003	.97

* β is the standardized regression coefficient.
MoCA = Montreal Cognitive Assessment
BMI = body mass index
MCIRS = Modified Cumulative Illness Rating Scale

Table 5. Cognitive Function, Measured by Mini Mental State Examination as Dependent Variable and 6-Min Walk Distance, Comorbidity Index, Pulmonary Function, and P_{aO_2} as Independent Variables

	Cognitive Function Values	
	β*	*P*
Intercept	$R^2 = 0.49$	<.001
Age	−0.21	.048
Male sex	0.40	<.001
Education level	0.40	<.001
BMI	−0.18	.11
6-Min walk distance	0.09	.42
MCIRS	−0.10	.39
FEV_1, % predicted	−0.11	.28
P_{aO_2}	−0.06	.53

* β is the standardized regression coefficient.
BMI = body mass index
MCIRS = Modified Cumulative Illness Rating Scale

of functional capabilities did not parallel the decline of cognitive function, although cognitive decline was faster in the presence of severe bronchial obstruction.[18] Clearly, further studies are warranted to elucidate this issue.

In the present study, none of the COPD severity measures, such as pulmonary function tests and arterial blood gases, showed any association with the risk of cognitive impairment. Previously, varying correlations between arterial blood gases, pulmonary function, and cognitive function were reported. In a cohort study of adults with COPD and referent subjects matched by age, sex, and race, none of the COPD severity measures were associated with the risk of cognitive impairment, consistent with our results. Conversely, low baseline S_{pO_2} was related to increased risk of cognitive impairment.[27] In a study involving 27 subjects with mild-to-moderate COPD, 35 subjects with severe COPD, and 27 controls, MMSE score positively correlated with P_{aO_2} in both the mild-to-moderate and severe COPD groups. Furthermore, MMSE scores correlated with FEV_1 in subjects with severe COPD.[2] In another study, 66 subjects with COPD were evaluated for neuropsychological functioning, and neuropsychological test battery scores showed a significant association with P_{aO_2} and with the degree of pulmonary impairment.[28] In subjects with hypoxic-hypercapnic COPD, cognitive impairment was significantly and positively correlated with age and duration of hypoxic-hypercapnic chronic respiratory failure.[17] In 18 subjects with COPD, measures of immediate and delayed memory, complex attention, and speed of information processing correlated highly with arterial carbon dioxide partial pressure and, to a lesser extent, with partial oxygen pressure.[29] In a study in 203 subjects with COPD, low-order significant inverse correlations were found between neuropsychologic impairment and P_{aO_2} and resting arterial oxygen saturation. The authors of that study concluded that cerebral disturbance is common in hypoxemic COPD and may be related in part to decreased availability of oxygen to the brain.[30] In another study, mildly, moderately, or severely hypoxemic subjects with COPD were compared with age- and ed-

ucation-matched subjects without COPD, where multivariate analyses revealed a consistent significant relationship between degree of hypoxemia and neuropsychologic impairment, but the amount of shared variance was small.[31] The discrepancy observed between these findings and ours may be related in part with the differences in disease severity, sample size, test methodologies, and the clinical characteristics of the subjects.

Certain limitations of our study have to be mentioned. First, a limited number of subjects with COPD were sampled. However, statistically significant and meaningful results were obtained in our study. Second, in this study, there was a wide age range among subjects with COPD, and age was an important determinant of cognitive dysfunction. However, educational status, 6-min walk distance, and sex emerged as important determinants of cognitive dysfunction independent of age. Another limiting aspect of the study is that we did not include a control group.

Conclusions

Subjects with COPD with better functional capacity and lower comorbidity index were found to have better cognitive function. The MoCA may be a more reliable screening test than the MMSE in detecting cognitive impairment in patients with COPD. The incorporation of cognitive tests into the general assessment of patients with COPD can provide further insights in terms of patient management.

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