The Evaluation of Cognitive Impairment and Relevant Factors in Patients with Chronic Obstructive Pulmonary Disease

Jing Li Yun Huang Guang-He Fei

Pulmonary Department, First Affiliated Hospital of Anhui Medical University, Hefei, China

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Key Words

Arterial blood gas • Chronic obstructive pulmonary disease • Clusterin • Cognitive performance • Pulmonary function

Abstract

Background: Chronic obstructive pulmonary disease (COPD) is understood to be a complex multicomponent disorder. The impairment of cognition is lasting and profound. However, the pattern of the cognitive decline and potentially adverse factors are poorly understood. **Objectives:** To evaluate the cognitive performances and the relevant factors in COPD patients and to investigate the relationship between cognition deficits and the classification of severity of the disease. **Methods:** Twenty-seven mild-to-moderate COPD patients, 35 severe COPD patients and 27 control subjects were recruited. Cognitive states were investigated by the Mini-Mental State Examination (MMSE). Pulmonary function, arterial blood gas and serum clusterin level were evaluated in each subject. **Results:** Lower MMSE score and higher serum clusterin concentration were observed in mild-to-moderate COPD patients, while the lowest MMSE score and the highest serum clusterin level were found in severe COPD patients when compared with control subjects. MMSE score is positively correlated with arterial oxygen tension and is inversely associated with serum clusterin level in both mild-to-mod-

erate and severe COPD patients. Furthermore, MMSE scores and serum clusterin concentrations were correlated with forced expiratory volume in 1 s in severe COPD patients. **Conclusion:** Cognitive impairment was found in COPD patients. It is associated with the classification of disease severity, hypoxemia and serum clusterin level. An increased serum clusterin level may be a relevant peripheral biomarker of cognitive dysfunction in COPD patients.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a primary airway inflammatory disease characterized by largely irreversible airflow limitation which results in hypoxemia and hypercapnia. Meanwhile, systemic inflammation has been considered to be one of the important factors linking COPD and related systemic manifestations [1–4]. The central nervous system, in particular, is vulnerable to hypoxemic insults and systemic inflammatory stress. Some studies have shown that COPD patients exhibit earlier cognitive decline in age and health status than expected [5, 6]. However, the mechanisms involved in the impairment of cognition and the relevant factors are complex and not fully understood [7, 8].

Clusterin, also known as apolipoprotein J, is expressed in most human tissues. It has two protein isoforms, namely a secreted heterodimeric glycoprotein and a truncated nuclear form [9]. Clusterin plays many roles in numerous cell types. Its effects are largely associated with its prominent ability to bind to hydrophobic regions of partially unfolded proteins, thus inhibiting protein aggregation and precipitation [10]. Previous studies have demonstrated that the peripheral clusterin level is elevated in several neuropathological conditions involving cognitive dysfunction and chronic inflammation of the brain [11]. Clusterin not only participates in the progression of pathological changes in incipient stages of mild cognitive impairment (MCI) but is also associated with the severity of Alzheimer's disease (AD) [12]. However, whether clusterin plays a role in the decline in cognition in COPD patients has not been reported.

In this study, we evaluated the cognitive performance and concentration of serum clusterin in COPD patients at different stages, as well as associations between the cognitive states, pulmonary function parameters, arterial blood gases and serum clusterin concentrations.

Material and Methods

Subjects

Eighty-nine subjects, including 27 mild-to-moderate COPD patients, 35 severe COPD patients and 27 control subjects, participated in the present study. The 3 groups were matched for age, sex, education level and body mass index (BMI). The COPD patients came from the First Affiliated Hospital of Anhui Medical University. The diagnosis and classification of COPD were made according to the Global Initiative for Chronic Obstructive Lung Disease 2010 guidelines [13]. All patients were treated only with necessary medications, i.e. antibiotics (levofloxacin, cefuroxime, amoxicillin/clavulanate potassium), β_2 adrenoreceptor agonists (salbutamol, salmeterol, terbutaline), ambroxol and oxygen therapy. Exclusion criteria were as follows: previous admission to an intensive care unit or an experience with mechanical ventilation, dementia, sleep disorders, obstructive sleep apnea, diabetes mellitus, head injury, psychiatric disorders (depression, anxiety disorders, schizophrenia or alcohol abuse) and use of any drugs which might affect cognitive performance (including anticholinergic medications, psychoactive drugs, long-acting benzodiazepines or tricyclic antidepressants, anticonvulsants, histamine H2 receptor antagonists and nonsteroidal anti-inflammatory agents). All participants were assessed by a complete physical examination by 3 raters including a respiratory physician, a cardiologist and a neuropsychologist. All subjects had given written informed consent to participate and were told of the possible risks of the study; the protocol was approved by the Human Investigation Committee of Anhui Medical University. The study was performed from February 1 to November 11, 2011.

Pulmonary Function Tests

Standardized pulmonary function tests were performed using a dry spirometer device (Erich Jaeger GmbH, Hoechberg, Germany). After inhaling salbutamol (Ventolin, GlaxoSmithKline, London, UK), each subject underwent a forced spirometry to obtain the following parameters: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁) and FEV₁/FVC ratio. Subjects with FEV₁ higher than 50% predicted but lower than 80% predicted were classified as the mild-to-moderate group; subjects with FEV₁ lower than 50% predicted were classified as the severe group according to Global Initiative for Chronic Obstructive Lung Disease 2010 criteria.

Arterial Blood Gas Analysis

The arterial oxygen tension (PaO₂), arterial carbon dioxide tension and blood oxygen saturation were evaluated for each subject using a Stat Profile Critical Care Xpress (Nova Biomedical, Waltham, Mass., USA) while patients breathed room air in the supine position.

Assessment of Cognitive Ability

The Mini-Mental State Examination (MMSE) was used to evaluate the cognitive function of each subject, whenever the subjects could cooperate adequately. This instrument explores spatial and temporal orientation, short- and long-term verbal memory, attention, verbal attention and practical ability in 12 items and 30 questions, enabling a rapid evaluation of cognitive status with a fairly high sensitivity, specificity and reproducibility (sensitivity 80–90%, specificity 80–100%). The correct answer to one question gives 1 score point (range 0–30). A score below 24 indicates MCI. All examinations were performed by a trained neuropsychologist.

Measurement of Serum Clusterin Concentration

Venous blood samples (5 ml) were centrifuged for 20 min at 3,000 rpm, and the supernatants were aliquoted and stored at –20°C until studied. A commercial enzyme-linked immunosorbent assay kit (R&D Biosystems, USA) was used for quantification of human clusterin concentration according to the manufacturer's instructions. The reference range of clusterin in human serum is 6.24–400 µg/ml. The intraassay and interassay variation coefficients were 3.4–3.7% and 7.2–8.4%, respectively. The established norm of serum clusterin level ranges from 90 to 220 µg/ml. All blood samples were collected around 6.30 a.m. in a regular examination room with the same lighting.

Statistical Analysis

The clinical characteristics of subjects were compared using a χ^2 test for categorical variables. Statistical significance of the differences between mean values from each group was tested using one-way analysis of variance for variables with normal distributions and a Kruskal-Wallis test otherwise. The Pearson correlation test was used to verify the relationship between numerical variables with normal distributions, while the Spearman rank correlation test was applied to nonparametric variables. The analysis was performed using Graphpad Prism 5. Values of $p < 0.05$ were considered to be significant.

Table 1. Demographic characteristics in the control group and mild-to-moderate and severe COPD groups

Characteristic	Control group (n = 27)	Mild-to-moderate COPD group (n = 27)	Severe COPD group (n = 35)	p value
Age, years	66.26 ± 7.08	70.48 ± 7.75	68.20 ± 7.82	0.13 ^a
Females/males, n	9/18	7/20	10/25	0.83 ^b
Smoking status, %				0.22 ^b
Never smoked	40.74	33.33	28.57	
Current smoker	33.33	18.52	17.14	
Exsmoker	25.93	48.15	54.29	
Cigarettes smoked, pack-years				
Current smoker	33.11 ± 12.97	32.00 ± 9.12	35.08 ± 12.26	0.90 ^a
Exsmoker	28.93 ± 7.35	30.85 ± 7.37	34.50 ± 4.10	0.16 ^a
Education, years	7.00 ± 4.92	6.78 ± 5.10	6.51 ± 4.96	0.93 ^a
BMI	23.59 ± 2.05	22.54 ± 3.48	21.96 ± 3.49	0.13 ^a
Cardiovascular disease, %	33.33	51.85	45.71	0.37 ^b

Data are presented as means ± SD, except where indicated otherwise. Cardiovascular disease includes hypertension, coronary artery disease and congestive heart failure.

^a One-way analysis of variance. ^b χ^2 test.

Table 2. Pulmonary function tests, cognitive state examination and the concentration of serum clusterin in the control group and mild-to-moderate and severe COPD groups

Test parameter	Control group (n = 27)	Mild-to-moderate COPD group (n = 27)	Severe COPD group (n = 35)	p value
FEV ₁ , % predicted	107.14 ± 15.88	60.52 ± 6.26**	34.95 ± 9.32**, ++	<0.01
FVC, % predicted	95.61 ± 14.89	76.62 ± 9.21**	55.44 ± 16.05**, ++	<0.01
FEV ₁ /FVC	90.02 ± 8.52	61.26 ± 6.24**	50.03 ± 11.43**, ++	<0.01
PaO ₂ , mm Hg	90.62 ± 6.52	73.13 ± 8.16**	67.54 ± 12.13**, ++	<0.01
PaCO ₂ , mm Hg	36.98 ± 2.86	38.29 ± 5.71*	47.37 ± 11.73**, ++	<0.01
SaO ₂ , %	97.50 (97.00–97.90) ^a	92.27 ± 3.17**	92.30 (89.70–95.10) ^a , **, +	<0.01 ^b
MMSE score	27.59 ± 2.89	24.78 ± 1.89**	22.94 ± 2.70**, ++	<0.01
Clusterin, µg/ml	121.30 ± 13.56	146.60 ± 13.90**	167.50 ± 18.13**, ++	<0.01

Data are presented as means ± SD. p values were calculated by one-way analysis of variance, except where indicated otherwise.

* p > 0.05, ** p < 0.01 vs. control group; + p > 0.05, ++ p < 0.01 vs. mild-to-moderate group. PaCO₂ = Arterial carbon dioxide tension; SaO₂ = blood oxygen saturation.

^a Medians (interquartile range). ^b Kruskal-Wallis test.

Results

Demographic Characteristics in the Control Group and Mild-to-Moderate and Severe COPD Groups

Demographic features of the control group and COPD groups are shown in table 1. The three groups were statistically similar with respect to age, sex, education level, smoking, BMI and cardiovascular disease. This statistical similarity reflected matching (p > 0.05 in all cases).

Relationship between COPD and the Risk of Cognitive Impairment

Table 2 shows that the MMSE score was significantly lower in the mild-to-moderate (p < 0.01) and severe COPD groups (p < 0.01) compared with the score in the control group. Furthermore, the MMSE score declined significantly in the severe group compared with that in the mild-to-moderate group (p < 0.01).

Table 3. Relationships between the relative test values and MMSE score in the groups with COPD of different severity

Test parameter	Mild-to-moderate COPD group MMSE (n = 27)		Severe COPD group MMSE (n = 35)		Total MMSE (n = 62)	
	r	p	r	p	r	p
PaO ₂	0.43	<0.05	0.39	<0.05	0.46	<0.01
PaCO ₂	0.32	0.10	0.01	0.96	0.04 ^a	0.78
SaO ₂	0.27	0.18	0.16 ^a	0.36	0.20 ^a	0.12
FVC	-0.13	0.52	0.19	0.27	0.31	<0.05
FEV ₁	0.07	0.72	0.46	<0.01	0.48	<0.01
FEV ₁ /FVC	0.28	0.16	0.16	0.37	0.33 ^a	<0.01
Clusterin	-0.45	<0.05	-0.55	<0.01	-0.61	<0.01

PaCO₂ = Arterial carbon dioxide tension; SaO₂ = blood oxygen saturation; r = Pearson correlation coefficient (except where indicated otherwise).

^a Spearman rank correlation coefficient.

Table 4. Relationships between the relative test values and the concentration of serum clusterin in the groups with COPD of different severity

Pulmonary function test parameter	Mild-to-moderate COPD group clusterin concentration (n = 27)		Severe COPD group cluster in concentration (n = 35)		Total clusterin concentration (n = 62)	
	r	p	r	p	r	p
PaO ₂	-0.61	<0.01	-0.34	<0.05	-0.48	<0.01
PaCO ₂	-0.22	0.28	0.15	0.38	0.13 ^a	0.31
SaO ₂	-0.27	0.18	-0.10 ^a	0.56	-0.22 ^a	0.08
FVC	0.15	0.46	-0.15	0.39	-0.38	<0.01
FEV ₁	0.06	0.78	-0.36	<0.05	-0.57	<0.01
FEV ₁ /FVC	0.19	0.35	-0.25	0.14	-0.37 ^a	<0.01

PaCO₂ = Arterial carbon dioxide tension; SaO₂ = blood oxygen saturation; r = Pearson correlation coefficient (except where indicated otherwise).

^a Spearman rank correlation coefficient.

Relationship between COPD and the Concentration of Serum Clusterin

Table 2 shows that the concentrations of serum clusterin increased significantly in the mild-to-moderate ($p < 0.01$) and severe COPD groups ($p < 0.01$) compared with the control group. Moreover, the serum clusterin concentration was significantly higher in the severe COPD group than that in the mild-to-moderate COPD group ($p < 0.01$).

Correlations among Cognitive Function, Pulmonary Function, Arterial Blood Gases and Serum Clusterin Level

Tables 3 and 4 show the correlations among MMSE scores, pulmonary function parameters, arterial blood

gases and the concentration of serum clusterin in COPD patients. The MMSE score was correlated with PaO₂ ($r = 0.43$, $p < 0.05$) and serum clusterin level ($r = -0.45$, $p < 0.05$) in the mild-to-moderate COPD group (fig. 1), while the MMSE score was associated with PaO₂, FEV₁ and serum clusterin concentration ($r = 0.39$, $p < 0.05$; $r = 0.46$, $p < 0.01$; $r = -0.55$, $p < 0.01$, respectively) in the severe COPD group (fig. 2). The MMSE score was further correlated with PaO₂, FEV₁ and serum clusterin concentration ($r = 0.46$, $p < 0.01$; $r = 0.48$, $p < 0.01$; $r = -0.61$, $p < 0.01$, respectively) and weakly associated with FVC and FEV₁/FVC ($r = 0.31$, $p < 0.05$; $r = 0.33$, $p < 0.01$, respectively) in the entire population of COPD patients (fig. 3, table 3). The other parameters were not significantly related with the MMSE score.

Fig. 1. Relationships and Pearson correlations between MMSE scores and the levels of PaO₂ (●) and serum clusterin concentrations (■) in the mild-to-moderate COPD group. PaO₂: $r = 0.43$, $p < 0.05$; clusterin: $r = -0.45$, $p < 0.05$.

Fig. 2. Relationships and Pearson correlations between MMSE scores and FEV₁% predicted (▲), the levels of PaO₂ (●) and serum clusterin concentrations (■) in the severe COPD group. PaO₂: $r = 0.39$, $p < 0.05$; FEV₁: $r = 0.46$, $p < 0.01$; clusterin: $r = -0.55$, $p < 0.01$.

Fig. 3. Relationships and Pearson correlations between MMSE scores and FEV₁% predicted (▲), the levels of PaO₂ (●) and serum clusterin concentrations (■) in the entire population of COPD patients. PaO₂: $r = 0.46$, $p < 0.01$; FEV₁: $r = 0.48$, $p < 0.01$; clusterin: $r = -0.61$, $p < 0.01$.

The serum clusterin concentration was negatively correlated with PaO₂ in the mild-to-moderate COPD group ($r = -0.61$, $p < 0.01$; fig. 4), whereas it was weakly related with both PaO₂ and FEV₁ in the severe COPD group ($r = -0.34$, $p < 0.05$; $r = -0.36$, $p < 0.05$, respectively; fig. 5). In addition, it was associated with PaO₂ and FEV₁ ($r = -0.48$, $p < 0.01$; $r = -0.57$, $p < 0.01$, respectively; fig. 6) and weakly correlated with FVC and FEV₁/FVC ($r = -0.38$, $p < 0.01$; $r = -0.37$, $p < 0.01$, respectively; table 4) in the entire population of COPD patients.

Discussion

In the present study, we observed overall significant cognitive deficits in COPD patients after we controlled for confounding factors, including smoking, education, BMI, sleeping and cardiovascular diseases known to affect cognition [14–19]. Therefore, consistent with previous reports, the results in the current study indicate that COPD is an independent risk factor for cognitive impairment [20–22]. We further detected that the global cognitive function was worse in severe COPD when compared to mild-to-moderate COPD. This observation shows for the first time that the cognitive decline is associated with the classification of severity during disease progression

in COPD patients and provides evidence for physicians to take effective actions to prevent and treat cognitive decline in patients in the early stage of COPD.

Chronic hypoxemia is one of the most important key mechanisms that can adversely affect neuropsychological and cognitive performance [23]. COPD patients exist in a state of persistent airflow limitation and often experience poor pulmonary function which leads to chronic hypoxemia. In our study, we examined the relationships between cognitive ability and pulmonary function or arterial blood gas in mild-to-moderate and severe COPD groups, respectively. We found that PaO₂ was positively correlated with cognitive ability in both groups. Consistent with our research, some earlier studies have also demonstrated that PaO₂ is correlated with cognitive function, particularly with regard to attention, motor function and processing speed [5]. These findings show that the chronic hypoxemia may be involved in the cognitive impairment in COPD patients.

Interestingly, as we explored these potential harmful factors for cognitive damage in the severe COPD group, we observed that cognitive ability is not only associated with the level of PaO₂ but is also positively linearly correlated with FEV₁. This was also shown in the entire population of COPD patients. Some prior studies have also demonstrated that a decline in FEV₁ level was related to

Fig. 4. Relationship and Pearson correlation between the concentrations of serum clusterin and the levels of PaO₂ in the mild-to-moderate COPD group. $r = -0.61$, $p < 0.01$.

Fig. 5. Relationships and Pearson correlations between the concentrations of serum clusterin and the levels of PaO₂ (●) and FEV₁% predicted (▲) in the severe COPD group. PaO₂: $r = -0.34$, $p < 0.05$; FEV₁: $r = -0.36$, $p < 0.05$.

Fig. 6. Relationships and Pearson correlations between the concentrations of serum clusterin and the levels of PaO₂ (●) and FEV₁% predicted (▲) in the entire population of COPD patients. PaO₂: $r = -0.48$, $p < 0.01$; FEV₁: $r = -0.57$, $p < 0.01$.

poor cognitive ability [24, 25]. However, other studies have shown that lung function is not a reliable predictor of cognitive function in COPD populations [26–28]. The precise mechanisms causing the phenomenon are still unknown. Some studies have proposed that intermittent and continuous hypoxia in COPD patients, which results from poor lung function, may lead to transient deficits in the metabolism of neurotransmitters in the central nervous system [29–32]. Other studies have suggested that in the late stage of the disease, as a consequence of decreased pulmonary function, cerebral blood perfusion is reduced, which may exacerbate ischemia in some brain regions and thus may increase subcortical atrophy [7, 33].

However, there was no correlation between cognitive ability and FEV₁ in the early stage of the disease in our present study. One possible explanation is that poor pulmonary function, hypoxia or systemic inflammation in the early stage of COPD were not as severe as in the later stage.

Recent studies have reported that MCI and AD patients have significantly higher serum clusterin levels than normal controls [11, 34]. The peripheral clusterin concentration was associated with MMSE score and brain atrophy in both MCI and AD patients [10, 12, 34]. Several lines of evidence further suggest biological roles of clusterin in pathways relevant to neuropathology, in-

cluding amyloid clearance, complement modulation and apoptosis [10]. In the present study, we evaluated the serum clusterin concentration and found that it is higher in COPD patients compared with that in control subjects. The pattern of the relationship between the elevated level of serum clusterin and the reduced cognitive ability in COPD patients was similar to that observed in MCI and AD patients [11, 34]. These findings indicate that COPD may be one of the basic diseases of preclinical AD. Since COPD patients not only have harmful factors such as hypoxemia but also evidence of systematic inflammation such as interleukin-6, interleukin-8 and tumor necrosis factor- α [1–3, 35], which spill over from the lung to the central nervous system, it is conceivable that some pathological changes occurring in the brain regions of COPD patients may increase the risk of AD. However, future studies are needed to address the precise mechanisms underlying this observation.

Furthermore, it is noteworthy that the level of serum clusterin was negatively correlated with cognitive ability. This finding suggests that the higher serum clusterin concentration may be a biologically relevant peripheral signature of cognitive impairment in COPD patients.

The cognitive impairment in COPD patients may occur in discrete domains. However, the MMSE, which has been proven useful and sufficient for cognitive measurements

[2], provides a broad scale and does separate the specific cognitive functions. A neuropsychological testing battery will be considered in future studies to provide detailed analysis and quantification of mental functions of patients such as short- and long-term memory, speech and learning impairments and impaired motor, visual and spatial functions. Another shortcoming of this study is the relatively small size of the participant population, which may partially account for the weak association between some of the measurements in our results. While the number of cases will be continuously increased in our future work, we anticipate that this study will lead to the realization of cognitive impairment in COPD patients in the field.

In conclusion, our experimental results confirmed that the cognitive impairment that occurs in COPD patients was significantly associated with disease severity, hypoxemia and serum clusterin concentration. Increased serum concentrations of clusterin may be a relevant peripheral signature of cognitive dysfunction in COPD pa-

tients. COPD characterized by chronic hypoxia and systematic inflammation may be one of the basic diseases of preclinical AD.

Acknowledgments

The authors would like to sincerely thank Rui Xu, Rong-huai Li and Xian-wei Hu for their assistance with the recruitment and clinical assessment of the participants. We thank Mr. Harsh Bhavsar from Rutgers University for careful editing of the manuscript.

Financial Disclosure and Conflicts of Interest

This work was supported by The National Natural Science Foundation of China (No. 81070020), The Natural Science Grant of Anhui Province (No. 090413119) and The Natural Science Grant of the Education Bureau of Anhui Province (No. KJ2008A158).

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