

Influencing Factors and Exercise Intervention of Cognitive Impairment in Elderly Patients with Chronic Obstructive Pulmonary Disease

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Abstract: Chronic obstructive pulmonary disease (COPD) is a common respiratory condition characterized by airflow limitation in the elderly. Airflow limitation is partially reversible and progressive. COPD not only causes a gradual decline in lung function but also affects the function of other systems throughout the body; it also has adverse effects on the central nervous system that can lead to cognitive impairment, especially in elderly patients. Therefore, understanding the influencing factors of cognitive impairment in elderly patients with COPD and applying early intervention are crucial in improving the quality of life of patients and reducing the burden on their families and society. This article mainly discusses the related factors of cognitive impairment in elderly patients with COPD and expands the possible mechanism of exercise in improving cognitive impairment in patients with COPD to provide a reference for the clinical prevention and treatment of cognitive impairment in elderly patients with COPD.

Keywords: chronic obstructive pulmonary disease, elderly people, cognitive function, influencing factors, exercise training

Introduction

COPD is a common disease of the airways resulting from exposure to noxious particles or gases, characterized by persistent respiratory symptoms and restricted airflow.¹ By 2020, COPD is projected to become the fifth leading cause of disability and the third leading cause of death worldwide.² Although it has been traditionally considered as a disease primarily affecting the lungs, COPD is often accompanied by many extra-pulmonary comorbidities such as heart failure, osteoporosis, muscle atrophy, and cognitive impairment.³ With the development of research in recent years, cognitive impairment associated with COPD has attracted considerable attention from scholars. The cognitive impairment not only affects the physical function and health status,⁴ but also aggravates mortality and disability in COPD patients.^{5,6} Studies have found that the mortality rate of elderly COPD patients with cognitive impairment is nearly three times higher than that of elderly patients with cognitive impairment or COPD,⁷ this phenomenon brings substantial economic burden on the patient's family and society.

Exercise training is a core element of pulmonary rehabilitation therapy of COPD.⁸ Studies have confirmed that it can effectively improve the cognitive function of elderly COPD patients and has many neuroprotective effects.⁹ However, current researches on exercise prevention and treatment of cognitive dysfunction in elderly patients with

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COPD is still in its infancy, and significant differences still exist in exercise doses. Thus, the results of different studies cannot be compared, and forming specific movement recommendations is difficult. Therefore, this paper aims to further explore the effect of exercise on cognitive impairment in elderly patients with COPD and its possible mechanism for providing guidance and reference for the exercise rehabilitation of cognitive impairment in elderly patients with COPD.

COPD and Cognitive Impairment

Cognition is a series of advanced activities in the cerebral cortex, including perception, storage, retrieval, and use of information; such activities enables individual behaviors to adapt to new situations and functions in the environment.¹⁰ Cognitive function includes many independent areas, such as memory, attention, executive ability, feeling, perception, thinking, learning and judgment.¹¹ When one or more of the above mentioned functions are impaired and affect the individual's activities of daily life, the patient has cognitive impairment. This type of impairment ranges from mild cognitive impairment to Alzheimer's disease.

Cognitive impairment is common in patients with COPD. The latest research shows that the prevalence rate of cognitive impairment in stable COPD patients is approximately 56.7%, which is four times higher than that in non-COPD patients.¹¹ It affects cognitive functions such as attention, memory, learning, psychomotor speed, visuospatial and motor structures, executive function and language skills in patients with COPD, with memory, attention, and executive function as the most common areas of impairment.^{12,13}

Neuroimaging studies have shown that certain brain regions decreased remarkably in patients with COPD, such as the volume of right inferior temporal gyrus, left orbital gyrus, right parahippocampal gyrus, right temporal lobe, bilateral caudate nucleus, bilateral anterior motor cortex, left superior marginal gyrus, and left insular gray matter.^{14–17} The damages of these brain regions are closely related to cognitive impairment in COPD patients. Chen et al pioneered the decomposition of the structure of the cerebral cortex into cortical thickness, surface area (SA) and cortical wrinkles to establish a complete profile of brain injury in COPD patients; and found the SA decreased in the motor, parietal and prefrontal cortex, especially in the dorsomedial prefrontal cortex and Broca's area.¹⁸ Therefore, cognitive dysfunction in COPD patients may be associated with overall and/or specific brain structural abnormalities.

Influencing Factors of Cognitive Impairment in Elderly Patients with COPD

Cognitive impairment in elderly patients with COPD is affected by various factors, including disease-specific factors such as hypoxemia,¹⁹ hypercapnia,²⁰ and systemic inflammation,²¹ and lifestyle factors such as diet deficiency,²² and lack of physical activity;^{23,24} Other factors, such as aging,²⁵ long-term smoking,^{26,27} education,²⁸ severity, and course of the disease,²⁹ may lead to abnormality in the brain structure and function in COPD patients, resulting in cognitive impairment. Moreover, elderly patients with COPD varying in degrees of synergy are often accompanied by cerebrovascular disease, anxiety and depression, sleep disorders, metabolic syndrome and other complications.³⁰ The main influencing factors of the development of elderly patients with COPD cognitive impairment include hypoxemia and hypercapnia, systemic inflammation, cerebrovascular disease, anxiety, and depression.

Hypoxemia and Hypercapnia

Peripheral airway obstruction and destruction of lung parenchyma reduce gas exchange in the lungs of patients with COPD, resulting in decreased oxygen supply and oxygenation, which finally lead to hypoxemia.³¹ The patients complicated with hypoxemia were in an anoxic state for a long time, and had decreased cerebral perfusion.³² When oxygen supply cannot meet the needs of brain metabolism, the microstructure of brain tissue may be damaged, including neuron damage and axonal degeneration.³³ Research has shown that around 77% of COPD patients with hypoxemia have cognitive impairment.³⁴ Meanwhile, longer duration of COPD could make the brain more vulnerable to hypoxic insults that can result in generation of free radicals, inflammation and neuronal damage.³⁵ Furthermore, patients with COPD tend to have hypercarbonic acidemia in the later stage of disease course due to the retention of carbon dioxide in the body and the increase of carbon dioxide concentration in the blood.³⁶ Hypercapnia can induce the production of oxygen-free radicals and block the synthesis of neurotransmitters such as acetylcholine, and result in overall neuronal damage.¹¹ Finally, Patients also show symptoms such as prolonged reaction time, slow information processing speed, delayed memory, and attention deficit.³⁷

Systemic Inflammation

The long-term pulmonary inflammatory response caused by COPD will break the balance of injury repair mechanism of the immune system, and the overflow of inflammatory mediators in the airway into the blood circulation leads to a systemic inflammatory response, and results in the damage to the structure and function of extrapulmonary organs.³⁸ Various immune cells and inflammatory mediators, including neutrophils, macrophages, interleukin-6 (IL-6), IL-8, tumor necrosis factor- α (TNF- α) and C-reactive protein (CRP), are involved in the occurrence and development of COPD.³⁹ The increase in IL-6 and CRP levels is related to the decrease in overall cognitive and executive functions.⁴⁰ This increase can cause secondary vascular cognitive impairment by participating in the occurrence of cardiovascular diseases such as atherosclerosis.²¹ Long-term inflammatory stimulation acts on the vascular endothelium, and results in vascular endothelial impairment, which leads to the destruction of blood-brain barrier function and structural changes in cerebral vessels of patients with COPD, and subsequently lead to the impairment of attention and memory of patients.⁴¹ Furthermore, to improve the inflammation, patients with COPD often use bronchodilators such as long-acting β -adrenoceptor agonist and long-acting muscarinic antagonist, which can also inhibit the central nervous system and cause damage to the attention function of COPD patients.¹⁰

Cerebrovascular Disease

A study found that elderly patients with COPD have a high risk of cerebral microhemorrhage.⁴² Cerebral microhemorrhage is an important imaging marker of Cerebral small vessel disease (CSVD) recently. CSVD is the microvascular lesion of white and gray matter, it is a group of pathological processes with a variety of etiology and pathogenesis,⁴³ that mainly involves small blood vessels such as cerebral arteries, veins and capillaries. Cerebral microhemorrhage can cause damage to the structural network of the brain,⁴⁴ and increase the risk of cognitive impairment.⁴⁵ Meanwhile, it is also associated with impaired executive function, attention and processing speed, and overall cognitive ability.⁴⁶ In addition, vascular inflammation can accelerate endothelial impairment and atherosclerosis. Arteriosclerosis can reduce vascular compliance, increase pulse pressure difference, and deliver increased blood flow to fine cerebral microvessels; Thus,

it causes microvascular brain damage and atrophy,⁴⁷ and ultimately decreases the cognitive ability of patients with COPD in terms of speed and executive function.⁴⁸

Anxiety and Depression

The respiratory function of elderly patients with COPD that has been seriously damaged for a long time, Meanwhile, a variety of factors including physical activity limitation, social activity impairment, physical deterioration, and social and economic factors' interaction, likely result in anxiety, depression and other negative emotions of COPD patients.⁴⁹ Studies have shown that more than one-third of COPD patients have comorbid symptoms of depression and anxiety.⁵⁰ Previous studies have also confirmed that anxiety and depression are independent risk factors and precursor symptoms of cognitive impairment,⁵¹ that can also cause morphological and functional changes in the medial amygdala, prefrontal cortex and hippocampus.⁵² Fritzsche et al also found that COPD patients with depression demonstrated clear cognitive impairment.⁵³ Other scholars have also found that the elderly with depression and anxiety showed poor speech fluency,⁵⁴ likely due to long-term depression in elderly patients with COPD. Depression will significantly reduce communication with the outside world, and patients with social communication dysfunction will affect their cognitive function.

Effects of Exercise on Cognitive Impairment in Elderly Patients with COPD

Exercise training is an essential part of pulmonary rehabilitation in patients with COPD.⁵⁵ Studies have shown that regular exercise can enhance the function of the central nervous system and reduce the risk of cognitive impairment.⁵⁶⁻⁵⁸ Emery et al found that exercise training for 20min can improve the performance of elderly COPD patients in language fluency tests.⁵⁹ Kozora et al found that after 3 weeks of exercise training, cognitive functions, such as visual attention, verbal memory and visual-spatial function in elderly patients with COPD improved.⁶⁰ Aquino et al also found that aerobic exercise combined resistance training for 4 weeks, twice a day for 30 min, can significantly improve the performance of cognitive areas including fluid intelligence, long-term memory, attention and reasoning in elderly patients with COPD.⁶¹ Furthermore, compared with elderly COPD patients who

Table 1 Effect of Exercise on Cognitive Impairment in Elderly Patients with COPD

Study	Characteristics of Participants	Exercise Intervention				Cognitive Indicators
		Duration	Type	Frequency	Intensity	
Emery et al, 1998 ⁶²	79 Subjects: EXESM group=29, age:65.4±6.4years, ESM group=25, age:67.4±5.9years, WL group=25, age:67.4±7.1years,	10 Weeks	First 5 weeks: 45minutes of aerobic exercise and strength training last 5 weeks: 60–90 minutes of aerobic exercise and strength training	5 times/week 3 times/week	Not specified	Attention motor speed mental efficiency * verbal processing*
Emery et al, 2001 ⁵⁹	58 Subjects: COPD group=29 age:67.8±7.4years, Healthy group=29 age:68.7±6.0years,	/	20 minutes of a modified bicycle ergometry stress test	Once	Began at 0 W and was increased 5 W every 2 min thereafter, with exercise rates remaining constant at 40 to 60 rpm.	Attention and memory mental efficiency motor speed verbal processing *
Enier et al, 2001 ⁶⁴	29 Subjects: age:68.1±6.0years, 15 subjects: Exercise group=8 age:67.1±3.9years, Control group=7 age:69.7±6.3years,	0-3 Months 3–18 Months	Walking: 30minutes; strength training: 2 sets of 15 repetitions	3 times/week	Dyspnea rating of 3–4 (moderate to somewhat hard)	Reasoning and problem-solving*
Kozora et al, 2002 ⁶⁰	59 Subjects: Exercise group=30 age:66.5years, Control group=29 age:66.9years,	3 Weeks	Exercise training	4 times/week	Not specified	Auditory and complex attention * sustained visual attention* complex visual-motor attention* immediate and delayed recall for verbal and nonverbal visual material * visuospatial function * naming to confrontation* verbal fluency* semantic fluency*

Pereira et al, 2011 ⁶⁷	34 Subjects: age:65.2±7years	3 Months	Aerobic training resistance training	3 times/week	Not specified	Selective attention cognitive flexibility, processing speed* phonemic and semantic fluency* short-term memory* verbal learning and memory*
Aquino et al, 2016 ⁶¹	28 Subjects: aerobic group=14 age:69.4±7.4years combined group=14 age:65.0±8.3years	4 Weeks	Aerobic training: 30 minutes resistance training: 3 sets of 4–10 repetitions	2 times/day, 5 days/week	Aerobic training: 70–90% of HRmax; resistance training: 70–90% of 1-RM	Selective and sustained attention* praxis abilities* abstract reasoning * verbal fluency*

Notes: Age are expressed as mean ± standard deviation; *Compared with pre-exercise intervention, there were significant improvements in the cognitive domain ($P<0.05$).

Abbreviations: EXESM, exercise, education and stress management; ESM, education and stress management but no exercise training; VWL, waiting list; RPD, rating of perceived dyspnea; HR_{max}, maximum heart rate; 1-RM, one repetition maximum.

did not receive exercise training, the language fluency of patients who underwent exercise training significantly improved after 10 weeks of training.⁶² Emery et al followed patients for 1 year after completing a 10-week exercise program and found that 39% of patients with continuous exercise maintained cognitive improvement, while those who stopped exercising showed cognitive decline.⁶³ Therefore, long-term and regular exercise training can reduce the incidence of cognitive impairment in elderly patients with COPD.

The exercise intervention programs for elderly COPD patients with cognitive impairment in some studies are described in the following sections (Table 1).

Possible Mechanism of Exercise on the Improvement Cognitive Impairment of Elderly Patients with COPD

As the main metabolic organ of oxygen, the brain has a large number of easily oxidized unsaturated fat, high levels of reactive oxygen species, therefore, the brain is particularly susceptible to oxidative damage.⁶⁵ Given the decrease in partial pressure of blood oxygen and brain hypoxia in patients with COPD, oxidative stress occurs easily, and results in the production of lipid peroxidation, which aggravates the damage in brain tissue and leads to the degeneration of brain neurons and cognitive dysfunction.⁶⁶ Studies have found that exercise can improve oxidative stress in patients with COPD. Lu et al determined that exercise can reduce the production of peroxynitrite, lipid peroxidation, and oxidative DNA damage.⁶⁵ Kwon et al also found that exercise increases the antioxidant defense response and protects against sleep deprivation and chronic cerebral lipid peroxidation, which reduced oxidative damage and improved cognitive function.⁶⁷ Therefore, exercise training play an positive role in affecting the anti-oxidative stress for the inhibition of the oxidative damage in lipids, proteins and nucleic acids, and also the contribution of neuroprotection and cognitive improvement.

Exercise has been increasingly recognized as a potential intervention for reducing chronic inflammation.^{68,69} Studies have shown that old people with exercise are less prone to systemic inflammation than older people without exercise.⁷⁰ Nascimento et al conducted a 16-week multi-mode physical exercise program for the elderly with cognitive impairment and found that exercise training can effectively reduce the

TNF- α level and improve their cognitive ability.⁷¹ As a critical anti-inflammatory cytokine, IL-10 inhibits systemic inflammation and plays a vital role in inhibiting the production of TNF- α .⁷² Chupel et al found that a 28-week program of strength training can improve the overall cognitive performance of older women with cognitive impairment by increasing the IL-10 levels and reducing the total white blood cell and lymphocyte counts.⁷³ Chupel et al also determined that 14 weeks of exercise training reduced the production of pro-inflammatory cytokines in older women, improved their chronic inflammation, and maintained the integrity of their blood-brain barrier; as a result, cognitive impairment slowed down.⁷⁴

The integrity of brain function is dependent on the continuous and steady blood supply of the cerebral circulation, especially the cerebral microvascular system. Compared with healthy subjects, the cerebral perfusion of the frontal and parietal lobes was significantly decreased in patients with COPD.⁷⁵ Exercise can up-regulate angiogenic factors such as vascular endothelial growth factor and insulin-like growth factor-1, and thus promote cerebral perfusion and improve the cognitive function.⁷⁶ Exercise can also enhance the efficiency of oxygen transport and utilization in the brain environment,⁷⁷ promote angiogenesis in parts of the brain and activate

additional brain regions that increase metabolic activity in the brain of COPD patients. Kramer et al found that exercise increased the utilization of oxygen and improved the performance of the elderly in functional tests.⁷⁸ In addition, increasing the flow of oxygen to the brain after exercise boosts the metabolism of neurotransmitters (norepinephrine [NE], acetylcholine, and dopamine [DA]) and factors that stimulate angiogenesis and synaptic development.⁷⁹ The process of neurogenesis, consequently promotes the production of neurotransmitters and their receptors to increase the brain's plasticity and reparability.⁸⁰

Exercise can enhance the metabolism of monoamine neurotransmitters, such as DA, 5-hydroxytryptamine, and NE, to improve the state of depression and the ability of information processing.⁸¹ Lin et al found that the anxiety and depression of COPD patients improved significantly after 3 months of walking training.⁸² Tselebis et al evaluated COPD patients with the Beck depression scale and found that 3 months of aerobic exercise significantly reduced the depression and anxiety scores.⁸³ Lavoie et al also found that anxiety and depression reduced with increases in either physical activity or exercise capacity, and cognitive function improved with increased exercise capacity, and cognitive function improved with increased exercise capacity in COPD patients.⁸⁴ Moreover, exercise

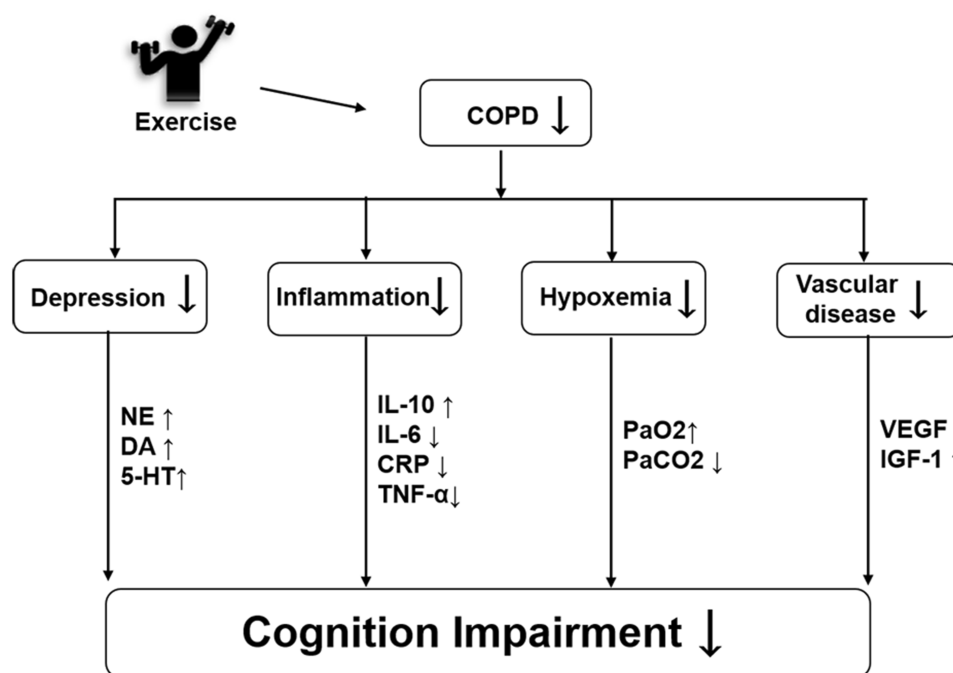


Figure 1 The possible mechanism of exercise improving cognitive impairment in the elderly with COPD.

Abbreviations: NE, norepinephrine; DA, dopamine; 5-HT, 5-hydroxytryptamine; IL-10, interleukin-10; IL-6, interleukin-6; CRP, C-reactive protein; TNF- α , tumor necrosis factor- α ; PaO₂, partial arterial blood oxygen pressure; PaCO₂, partial arterial carbon dioxide pressure; VEGF, vascular endothelial growth factor; IGF-1, insulin-like growth factor-1.

can change the structure of the central nervous system, specifically by changing the plasticity of the cerebral cortex, slowing the atrophy of gray and white matter, changing the structure and function of the frontal, parietal and temporal lobes of the brain,⁸⁵ and increasing the volume of hippocampus,⁸⁶ to maintain the stability in cognitive function of patients with COPD. Therefore, increasing exercise capacity can improve psychological and cognitive outcomes in patients with COPD. In summary, exercise can improve cognitive performance in elderly patients with COPD through multiple pathways, such as improving oxidative stress, systemic inflammation, cerebrovascular function, and anxiety and depression. Meanwhile, the mechanism of the cognitive improvement caused by exercise intervention needs to be further studied and combined with the mechanism of the occurrence and development of cognitive impairment to explain its neuropathological process fundamentally.

Figure 1 show the possible mechanism of exercise improving cognitive impairment in the elderly with COPD.

Conclusion

The Cognitive dysfunction is a common complication of COPD, which is related to hypoxemia, hypercapnia, systemic inflammation, anxiety and depression. These factors lead to abnormal brain structure and function, and finally cause the manifestation of the symptom of cognitive function impairment in the elderly COPD patients. As most of the patients with COPD are old and have long suffered with the disease, cognitive impairment will not only affect the quality of life of the patients but also bring significant challenges to the medical and health system. Exercise training, which is a core element of COPD lung rehabilitation, can reduce the cognitive impairment of COPD patients through many ways, which are important in improving the quality of life of elderly COPD patients.

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Disclosure

The authors report no conflicts of interest in this work.

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